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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

Graceway Pharmaceuticals, LLC, and 3M Innovative Properties Company, Plaintiffs, v. Perrigo Company, Perrigo Israel Pharmaceuticals Ltd., and Nycomed U.S., Inc., Defendants.	Civil Action No. 2:10-cv-937 (WJM-MF) The Honorable William J. Martini **Motion Day: April 19, 2010** **ORAL ARGUMENT REQUESTED**

DECLARATION OF CHARLES W. STOTTER IN OPPOSITION TO NYCOMED'S MOTION TO DISMISS PURSUANT TO RULE 11

Charles W. Stotter, an attorney duly admitted to practice before this U.S. District Court and in the State of New Jersey, declares the following under the penalty of perjury:

1. I am an attorney at Edwards Angell Palmer & Dodge LLP, counsel for plaintiffs, and am familiar with the facts and circumstances of this litigation.

2. Attached hereto as Exhibit 1 is a true and correct copy of the relevant pages from the Transcript of Proceedings dated March 2, 2010, on the hearing in this action regarding Plaintiffs' Motion for Interim Relief.

3. Attached hereto as Exhibit 2 is a true and correct copy of the Declaration of Michael Nordsiek previously filed in this action in support of Plaintiffs' Motion for Interim Relief.

4. Attached hereto as Exhibit 3 is a true and correct copy of the publication entitled Draft Guidance for Industry: *Citizen Petitions and Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act* (Jan. 2009).

5. Attached hereto as Exhibit 4 is a true and correct copy of a response by the Food and Drug Administration to a Citizen Petition, bearing Docket No. 2005P-0127 (Sept. 13, 2005).

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed on: April 5, 2010

/s/ Charles W. Stotter
Charles W. Stotter

EXHIBIT 1

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
Criminal No. 2:10-cv-00937-SDW-MCA

GRACEWAY PHARMACEUTICALS, LLC, 3M INNOVATIVE PROPERTIES COMPANY,	:	TRANSCRIPT OF PROCEEDINGS - TRO Application -
vs.	:	
PERRIGO COMPANY, PERRIGO ISRAEL PHARMACEUTICALS LTD, NYCOMED U.S., INC.	:	
Defendants.	:	

Newark, New Jersey
March 2, 2010

B E F O R E:

THE HONORABLE WILLIAM J. MARTINI,
UNITED STATES DISTRICT JUDGE

Pursuant to Section 753 Title 28 United States Code, the following transcript is certified to be an accurate record as taken stenographically in the above entitled proceedings.

S/WALTER J. PERELLI

WALTER J. PERELLI, CCR, CRR
Official Court Reporter

A P P E A R A N C E S:

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ALBERT B. CHEN, ESQ.
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CARELLA, BYRNE, CECCHKI, OLSTEIN,
BRODY & AGNELLO, PC
BY: ERIC MAGNELLI, ESQ.
Attorneys for Defendant Perrigo Company & Perrigo Israel
Pharmaceuticals Ltd.

we -- the varieties of it that we can get commercially to see whether those -- all the commercially available, you know, that's suitable for use with humans, we've done subsequent testing just to try to make sure that we're right that the formulation must be covered. And everything we know and everything our scientists know say that their formulation is covered by our patent claims.

We've provided your Honor the Declaration of Michael Nordsiek, who is head of product development at Graceway. He's here in the courtroom, your Honor, if the Court had any questions for him. He's present here in the courtroom and perfectly willing to answer questions. He submitted a declaration, attached a claim chart. We went through a number of the claims of the patent and he's explained why we believe each limitation of each of those claims is met by Nycomed's product. I'd be happy, your Honor, to walk through one of the claim charts if your Honor would like.

THE COURT: Before we do that or before we even consider that, let me ask counsel for the Defendant, Mr. Moore is it?

MS. MOORE: I'm Moore.

THE COURT: I'm sorry. Mr. Rhoads.

MR. RHOADS: Don Rhoads, your Honor.

THE COURT: Okay, Mr. Rhoads.

Counsel just pointed out in your submission that the

only reference you make to disputing that you infringe is on page 3 where you say:

"Graceway cannot succeed on the merits because Nycomed's product does not infringe a single claim of the Patent-in-Suit."

She's quite right, I don't know if you get into too much more detail. I know you argue that it's invalid and it's obvious, but as far as the claims itself, you're disputing and saying you don't infringe on any of the Plaintiffs' claims, your patent -- the patent claims. Correct?

MR. RHOADS: Yes. We believe we do not infringe.

But if I may point the Court to the '672 Patent claims I'll explain what's going on and why we filed a Rule 11 motion against this entire suit.

I wasn't going to bring that up. Under Rule 11(c) we're not supposed to file that with the Court. But when you see the claims, your Honor, there's no way they could have a good faith basis to allege infringement.

Are we up, Mr. Lee?

MR. LEE: Yes.

MR. RHOADS: If you could bring up Exhibit 2, which is the '672 Patent, and go to the claims.

You know what, maybe we should first start with Table 1 of the '672 Patent.

(Utilizing PowerPoint presentation.)

super-refined oleic acid. Right?

MR. RHOADS: Yes.

THE COURT: And that is what the plaintiff claims is in their patent. Correct?

MR. RHOADS: Yes. So they must have bought this around 2004. So whatever you called super-refined oleic acid in 2004 must be what they used.

Now, if we go two the claims, if we could go to the claims --

THE COURT: You don't -- you acknowledge that you use oleic acid?

MR. RHOADS: We've told them that.

THE COURT: Okay.

MR. RHOADS: They know that. They got that in January 2007. Our formulation --

THE COURT: Your contention is that your formulation is different than the super oleic acid?

MR. RHOADS: Well, we'll go to the claims and I'll show you exactly what our contention is. Because the claims don't require super-refined oleic acid.

Could you go to Claim 1, please.

There's three independent claims here.

So if you don't infringe the three independent claims, you can't infringe any of them because dependent claims just add more restrictions.

You can't guess that it would have these impurities --

THE COURT: When was your cream first put out in the market?

MR. RHOADS: On the 25th.

THE COURT: Okay.

MR. RHOADS: But it wouldn't have been stored under those conditions. So they would have to actually get a batch that we made, then store it for 15 days --

THE COURT: I mean, part your argument is they could not have gotten a batch prior to the 25th?

MR. RHOADS: They couldn't have gotten a batch. We don't sell batches, we sell finished product.

THE COURT: Okay.

MR. RHOADS: So it's basically impossible. You can't intuitively see that we have these impurities.

Why not?

Because of that Table 1.

And maybe bring up Table 2 now.

So Table 1 tells what you the formulations are. Table 2 shows you the results. And it's those results of the impurities that are their invention. And the differences are very fine.

So the differences between oleic acid in A and B and whatever they bought in 2004 and they're calling super-refined oleic acid in C and D, these aren't really big differences.

you're right on all this and if they infringed and if you're right on this argument, the damages could be compensable and they could be computed. So that's why I'm wondering: Where is the irreparable harm that requires an injunction or a temporary restraint?

MS. MOORE: Okay. I was looking more at what the --

THE COURT: No. I'm almost -- in terms of showing that you've made at this preliminary stage that there's a likelihood of your succeeding on the merits that there was an infringement of the '672 Patent, subject to some further reflection I'm inclined to think you've met that burden. I'm having a more difficult time with why you need a restraint. I think you can compute damages. If you're right and they're wrong, they lose on the case, you'll be able to compute what your losses in damages were --

MS. MOORE: But that --

THE COURT: -- either way. You'd either make your argument and have a hearing on your lost profits on Aldara, or whatever they gained by way of marketing this product you should recover.

MS. MOORE: But there are lots of elements of damage here that are covered by Mr. Moccia's Declaration which the courts, this Court, the Federal Circuit have deemed to be not easily quantifiable, not easily calculable.

THE COURT: Again, tell me briefly --

EXHIBIT 2

UNITED STATES DISTRICT COURT FOR THE
DISTRICT OF NEW JERSEY

Graceway Pharmaceuticals, LLC and 3M Innovative Properties Company, Plaintiffs, vs. Perrigo Company, Perrigo Israel Pharmaceuticals Ltd., and Nycomed U.S. Inc., Defendants.	Civil Action No. 10-cv-0937 The Honorable Susan Davis Wigenton **DECLARATION OF MICHAEL NORDSIEK IN SUPPORT OF PLAINTIFFS' MOTION FOR INTERIM RELIEF**

I, Michael T. Nordsiek, hereby declare as follows:

1. I am the Executive Vice President of Product Development at Graceway Pharmaceuticals LLC ("Graceway"), and I have held that position since January 1, 2007.

2. Prior to joining Graceway, I held product development related positions at a number of pharmaceutical companies including ICI Pharmaceuticals Group, Rhone-Poulenc Rorer Pharmaceuticals, CIBA Self-Medication, Dermik Laboratories, Inc (a subsidiary of Aventis Pharmaceuticals), Bioglan Pharmaceuticals Company and Chester Valley Pharmaceuticals. A copy of my CV is attached hereto as Exhibit A.

3. In 1981, I graduated with a B.S. in Pharmacy from West Virginia University, and I completed approximately three years of graduate studies in chemical engineering and pharmaceutics at Drexel University.

4. I have over twenty five years of pharmaceutical formulation experience in the pharmaceutical industry.

5. For the last three years I have been working almost exclusively with imiquimod

and formulations thereof. In my opinion, imiquimod is a very stable molecule and is one of the most stable molecules with which I have worked in all my years of experience in pharmaceutical development and formulation.

6. I have been told that in order to directly infringe a patent claim, every limitation of that claim must be present in the accused product. If even one claim limitation is missing from the accused product, it will not directly infringe.

7. I have been told that in order to determine whether an accused products infringes a patent, I should give the claims their ordinary meaning as understood by a person of skill in the art unless defined in the patent.

8. I have also been told that even if a claim limitation is not literally present in an accused product, it may be present by equivalence. I have been told that an element of an accused product may be considered equivalent to a claim element in a patent if the differences between the two are "insubstantial." I have been told that in determining whether an aspect or element of an accused product is equivalent to a claim limitation, courts will often consider the following three factors: 1) whether they perform the same function, 2) whether they perform that function in the same way, and 3) whether they achieve the same result. I have been told that this is sometimes referred to as the "function/way/result" test. I have been told that differences with respect to any one of the three prongs of the "function/way/result" test may cause something to be considered not equivalent to a claim limitation.

9. I have reviewed U.S. Patent No. 7,655,672 ("the '672 Patent") and the issued claims. (Exhibit B, attached hereto).

10. I understand that Nycomed has filed an Abbreviated New Drug Application (ANDA). By filing an ANDA, Nycomed has asserted that its generic imiquimod-oleic acid

cream is bioequivalent to Aldara®. As I further understand, approval by the Food and Drug Administration (FDA) of Nycomed's generic imiquimod-oleic acid cream indicates that the FDA has determined that Nycomed's generic imiquimod-oleic acid cream covered under Nycomed's ANDA is bioequivalent to Aldara®.

11. In my opinion, because FDA has determined that Nycomed's generic imiquimod-oleic acid cream is bioequivalent to branded Aldara®, Nycomed's generic imiquimod-oleic acid cream must be a pharmaceutical cream for topical application to a dermal or mucosal surface for topical delivery of imiquimod.

12. In my opinion, because FDA has determined that Nycomed's generic imiquimod-oleic acid cream is bioequivalent to branded Aldara®, Nycomed's generic imiquimod-oleic acid cream must include a therapeutically effective amount of imiquimod.

13. I have reviewed the formulation for generic imiquimod-oleic acid cream that Nycomed provided to Graceway in a January 10, 2007 letter. (Exhibit C, attached hereto). This letter reports that Nycomed's generic imiquimod-oleic acid cream is formulated with an oleic acid component. Because FDA has determined that Nycomed's generic imiquimod-oleic acid cream is bioequivalent to branded Aldara®, Nycomed's generic imiquimod-oleic acid cream must contain a pharmaceutically acceptable vehicle that includes the oleic acid component.

14. Substances denominated "oleic acid" are not 100% pure "oleic acid," and generally contain additional substances such as, linoleic acid and other impurities. These substances may affect the stability of the oleic acid within the oleic acid component, the active ingredient and the stability of the overall pharmaceuticals formulated with oleic acid.

15. In my opinion, Nycomed's generic imiquimod-oleic acid cream cannot be formulated with an oleic acid component that is unstable. In order to be sufficiently stable,

Nycomed's generic imiquimod-oleic acid cream must be formulated with an oleic acid component that is of a refined grade.

16. As I understand, an oleic acid component that has not been refined contains high levels of polar impurities, such as peroxides, and thus is not a suitable excipient for use in topical pharmaceutical formulations due to its inherent variability in quality and its oxidative instability. Such impurities lead these oleic acid components to degradation and rancidity upon exposure to air, even at ambient temperature conditions. For this reason, an oleic acid component that has not been refined or suitably stabilized is not a commercially viable excipient for an imiquimod formulation.

17. A refined grade of an oleic acid component, in my opinion, comprises at least about 80% oleic acid by weight as a fatty acid with a peroxide value of less than about 5 milliequivalents of oxygen per kilogram and less than about 1% by weight polar impurities.

18. All of the independent claims in the '672 Patent (i.e. Claims 1, 7, and 13) define oleic acid as being refined to the parameters set forth in ¶ 17. By defining the oleic acid component as being refined to these parameters, these claims in the '672 Patent effectively define the stability of the oleic acid component of the claimed formulation.

19. In my opinion, for the oleic acid component in Nycomed's generic imiquimod-oleic acid cream to be stable, it must comprise at least about 80% oleic acid by weight as a fatty acid, have a peroxide value of less than about 5 milliequivalents of oxygen per kilogram, and contain less than about 1% by weight polar impurities.

20. Because imiquimod is such a stable molecule, it is my opinion that Nycomed's generic imiquimod-oleic acid cream formulation will have imiquimod-related impurities in an amount of no more than about 0.03% by weight after storage of Nycomed's generic imiquimod-

oleic acid cream at ambient conditions for 15 days. This is confirmed by the data in Table 2 of the '672 Patent.

21. Table 2 of the '672 Patent provides data on imiquimod-related impurities for certain oleic acid formulations of imiquimod. I have compared the excipients identified for the imiquimod-oleic acid cream formulations tested in Table 2 (columns C and D) of the '672 Patent (Exhibit B) with the excipients identified by Nycomed as being present in its generic imiquimod-oleic acid cream formulation covered under its ANDA (Exhibit C). It is my view that the excipients in Nycomed's generic imiquimod-oleic acid cream formulation are the same as those reported in Table 2 (columns C & D) of the '672 Patent.

22. It is my further view that the oleic acid component in Nycomed's generic imiquimod-oleic acid cream formulation and the oleic acid component in the imiquimod-oleic acid cream formulations reported in Table 2 (columns C and D) of the '672 Patent each comprise at least about 80% oleic acid by weight as a fatty acid with a peroxide value of less than about 5 milliequivalents of oxygen per kilogram and less than about 1% by weight polar impurities.

23. While there are some very slight differences in the amount of excipients between the imiquimod-oleic acid cream formulations tested in Table 2 (columns C and D) in the '672 Patent (Exhibit B) and Nycomed's generic imiquimod-oleic acid cream formulation, these minor quantity differences would have no impact on the amount of imiquimod-related impurities because the excipients are the same.

24. Because it is my belief that Nycomed's generic imiquimod-oleic acid cream formulation contains the same excipients as reported in Table 2 (columns C and D) of the '672 patent and an oleic acid component refined as described in ¶ 17 above, and because imiquimod is a very stable molecule, it is my belief that Nycomed's generic imiquimod-oleic acid cream will

have:

(a) imiquimod-related impurities in an amount of no more than about 0.03% by weight after storage of Nycomed's generic imiquimod-oleic acid cream at ambient conditions for about 15 days;

(b) imiquimod-related impurities in an amount of no more than about 0.15% by weight after storage for at least about 2 months at 40° C. and at about 75% humidity. Based on the data in Table 2 of the '672 Patent, an imiquimod cream formulation formulated with a refined grade oleic acid will have this characteristic;

(c) imiquimod-related impurities in an amount of no more than about 0.29% by weight after storage for at least about 4 months at 40° C. and at about 75% humidity;

(d) imiquimod-related impurities in an amount of no more than about 0.04% by weight after storage for at least about 2 months at 40° C. and at about 75% humidity;

(e) imiquimod-related impurities in an amount of no more than about 0.04% by weight after storage for at least about 4 months at 40° C. and at about 75% humidity; and

(f) imiquimod-related impurities in an amount of no more than about 0.15% by weight after storage for at least about 4 months at 40° and about 75% humidity.

25. Based on my review of the formulation Nycomed provided in its January 10, 2007 letter, Nycomed's generic imiquimod-oleic acid cream includes about 5% by weight imiquimod and about 25% by weight an oleic acid component. Thus, Nycomed's generic imiquimod-oleic acid cream has been formulated with no more than about 10% by weight imiquimod (it contains 5%) and an oleic acid component of no more than about 40% by weight (it contains 25%).

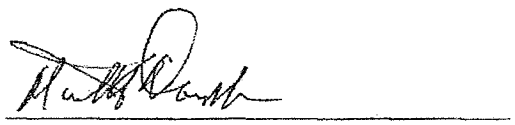
26. Based on my review of the formulation Nycomed provided in its January 10, 2007 letter, Nycomed's generic imiquimod-oleic acid cream includes no more than about 5% by

weight imiquimod (it contains 5%) and an oleic acid component of no more than about 30% by weight (it contains 25%).

27. Based on the foregoing, it is my opinion that every limitation of at least Claims 1, 5, 7, 11, 13, 17 and 19-20 of the '672 Patent are met by Nycomed's generic imiquimod-oleic acid cream. It is thus my opinion that Nycomed' generic imiquimod-oleic acid cream formulation literally infringes the '672 Patent. For ease of reference, attached hereto as Exhibit D is a claim chart which sets forth the conclusions expressed in this declaration in chart form.

28. I have personal knowledge of the matters discussed herein. If called upon, I am competent to testify to the preceding statements. I declare under penalty of perjury under the laws of the United States of America and the State of New Jersey that the foregoing is true and correct.

Executed this 28th day of February, 2010.



Chester County, Pennsylvania

Michael Nordsiek
EVP, Graceway Pharmaceuticals

EXHIBIT A

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4/25/09

PROFESSIONAL PROFILE:

Over twenty-five years experience in the pharmaceutical industry with a strong technical knowledge and management background pertaining to Rx products in the following areas:

- Formulation and Process Development of liquid, semi-solid, solid and controlled release dosage forms
- Pilot and production scale manufacturing and packaging of parenterals, liquids, aerosols, suspensions, ointments, lotions, creams, tablets, capsules, etc.
- Raw material characterization and evaluation
- Management of Professional and Organized Labor employees
- Good Manufacturing Practices within pilot and production environments
- Compiling of INDs, CMC/NDAs, ANDAs and supplements to NDAs
- FDA pre-approval and cGMP Inspections
- Product supply chain management

PROFESSIONAL EXPERIENCE:

GRACEWAY PHARMACEUTICALS, LLC, Exton, PA
Current Executive Vice President of Product Development (January 2007 – present)

Key responsibilities include:

- Establishment of the necessary processes and procedures as well as personnel recruitment and development for Regulatory Affairs, and Product Development Departments
- Development of new products and line extensions using internal and/or external resources
- Process Development and Scaleup of products from research into production
- Introduction of new process, equipment and packaging technologies into production
- Reformulation of existing products for quality and/or process improvements
- Process and Analytical Method Technology transfer of products worldwide
- Evaluation of new product licensing, joint venture, etc. opportunities
- Manufacture of clinical dosage form supplies
- Evaluation of alternate supplier raw material programs
- Product cost of goods reduction programs
- Administration and Development of assigned staff personnel, budgets, and policies to support Product Development Activities

CHESTER VALLEY PHARMACEUTICALS, Malvern, PA
Sr. Vice President, Technical Operations and Product Development (November 2004 – December 2006)

Key responsibilities include the start-up and on-going management of Quality, Product Development, Validation and Technical Operation activities supporting Chester Valley Pharmaceuticals Company.

BIOGLAN PHARMACEUTICALS COMPANY, Malvern, PA
Vice President, Technical Operations and Product Development (December 1999 – October 2004)

DERMIK LABORATORIES, INC. (subsidiary of AVENTIS PHARMACEUTICALS, formerly RHÔNE-POULENC RORER), Collegeville, PA
Director, Pharmaceutical Development (May 1996 – December 1999)

CIBA SELF-MEDICATION, Ft. Washington, PA
Director, Product Development (March 1995 – May 1996)

RHÔNE-POULENC RORER PHARMACEUTICALS, Ft. Washington, PA
Director, Product Development Consumer Products (June 1994 – February 1995)
Director, Secondary Manufacturing (Kankakee, IL) (March 1992 – May 1994)
Department Manager, Technical Support (June 1990 – February 1992)

ICI PHARMACEUTICALS GROUP, Newark, DE
Manager, Process Development (June 1988 – June 1990))
Group Leader, Process Development (February 1986 – June 1988)

MERCK, SHARP AND DOHME, West Point, PA
Staff Pharmacist, Research & Development (December 1984 – February 1986)
Pharmacist, Pharmaceutical Mfg. Technical Service (March 1982 – November 1984)
Quality Control Inspector (May 1981 – March 1982)

EDUCATION: West Virginia University, WV
B.S. Pharmacy (1976 – 1981)
GPA 3.3/4.0
Graduate courses in Chemical Engineering and Pharmaceutics

PERSONAL INTERESTS: Family activities, running, swimming, golf and tennis

REFERENCES: Furnished upon request.

EXHIBIT B

US007655672B2

(12) **United States Patent**
Statham et al.

(10) **Patent No.: US 7,655,672 B2**
(45) **Date of Patent: *Feb. 2, 2010**

(54) **IMMUNE RESPONSE MODIFIER FORMULATIONS CONTAINING OLEIC ACID AND METHODS**

(75) Inventors: **Alexis S. Statham**, Woodbury, MN (US); **Robert J. Nelson**, Cottage Grove, MN (US)

(73) Assignee: **3M Innovative Properties Company**, St. Paul, MN (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **12/334,255**

(22) Filed: **Dec. 12, 2008**

(65) **Prior Publication Data**

US 2009/0093514 A1 Apr. 9, 2009

Related U.S. Application Data

(63) Continuation of application No. 11/276,324, filed on Feb. 24, 2006, which is a continuation of application No. 11/303,659, filed on Dec. 16, 2005, now abandoned.

(60) Provisional application No. 60/636,916, filed on Dec. 17, 2004.

(51) **Int. Cl.**
A01N 43/42 (2006.01)
A01N 43/52 (2006.01)

(52) **U.S. Cl.** **514/290**; 514/393

(58) **Field of Classification Search** 514/290, 514/393

See application file for complete search history.

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Primary Examiner—Sreeni Padmanabhan
Assistant Examiner—Renee Claytor
(74) *Attorney, Agent, or Firm*—Edwards Angell Palmer & Dodge LLP

(57) **ABSTRACT**

Pharmaceutical formulations and methods including an immune response modifier (IRM) compound and an oleic acid component are provided where stability is improved by using oleic acid have low polar impurities such as peroxides.

20 Claims, No Drawings

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IMMUNE RESPONSE MODIFIER FORMULATIONS CONTAINING OLEIC ACID AND METHODS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims benefit of U.S. provisional application 60/636,916, filed Dec. 17, 2004, and Ser. No. 11/303,659 filed Dec. 16, 2005, the contents of which are hereby incorporated by reference.

FIELD OF THE INVENTION

The present invention relates to pharmaceutical formulations for the topical or transdermal delivery of immunomodifying drugs.

BACKGROUND

There has been a major effort in recent years, with significant success, to discover new drug compounds that act by stimulating certain key aspects of the immune system, as well as by suppressing certain other aspects. These compounds, referred to herein as immune response modifiers (IRMs), appear to act through immune system mechanisms known as toll-like receptors to induce selected cytokine biosynthesis. They may be useful for treating a wide variety of diseases and conditions. For example, certain IRMs may be useful for treating viral diseases (e.g., human papilloma virus, hepatitis, herpes), neoplasias (e.g., basal cell carcinoma, squamous cell carcinoma, actinic keratosis, melanoma), and TH2-mediated diseases (e.g., asthma, allergic rhinitis, atopic dermatitis), and are also useful as vaccine adjuvants.

Many of the IRM compounds are small organic molecule imidazoquinoline amine derivatives (see, e.g., U.S. Pat. No. 4,689,338), but a number of other compound classes are known as well (see, e.g., U.S. Pat. Nos. 5,446,153, 6,194,425, and 6,110,929) and more are still being discovered.

One of these IRM compounds, known as imiquimod, has been commercialized in a topical formulation, ALDARA, for the treatment of actinic keratosis, basal cell carcinoma, or anogenital warts associated with human papillomavirus.

Pharmaceutical formulations containing IRM compounds are disclosed in U.S. Pat. Nos. 5,238,944; 5,939,090; and 6,425,776; European Patent 0 394 026; and U.S. Patent Publication 2003/0199538.

Although some of the beneficial effects of IRMs are known, the ability to provide therapeutic benefit via topical application of an IRM compound for treatment of a particular condition at a particular location may be hindered by a variety of factors. These factors include: irritation of the skin to which the formulation is applied; formulation wash away; insolubility of the IRM compound in the formulation; chemical degradation of the IRM compound and/or other ingredients, physical instability of the formulation (e.g., separation of components, thickening, precipitation/agglomerization of active ingredient, and the like); poor permeation; and undesired systemic delivery of topical IRM formulations if not intended to be transdermal.

Accordingly, there is a continuing need for new and/or improved IRM formulations.

SUMMARY

It has now been found that, while oleic acid can be used to solublize IRMs, even difficult to formulate, highly insoluble IRMs, formulations comprising an IRM compound in combination with oleic acid can suffer from impaired stability. Somewhat surprisingly, addition of greater amounts of antioxidants to the formulation does not solve the problem. However, it has been found that utilizing an oleic acid component having reduced amounts of polar impurities, such as peroxides, aldehydes, alcohols, and ketones in a formulation containing an IRM can reduce the formation of impurities and thereby provide improved formulation stability. Instability is an important issue for pharmaceutical formulations and can reduce the shelf life of a product or jeopardize regulatory approvability.

It has been discovered that the stability of a formulation containing an IRM compound and oleic acid can be improved by utilizing an oleic acid component that is free of or contains low amounts of polar impurities, such as peroxides, aldehydes, alcohols, and ketones. Although not intending to be bound to any particular theory or mechanism, it is hypothesized that the higher amounts of polar impurities present in the oleic acid component can react with the IRM compound, thereby destabilizing the formulation and increasing the rate of formation of impurities derived from the IRM compound.

In one aspect, the present invention provides a pharmaceutical formulation comprising a therapeutically effective amount of an immune response modifier (IRM) compound and a pharmaceutically acceptable vehicle including an oleic acid component, wherein the formulation is substantially free of polar impurities introduced by the oleic acid component.

In another aspect, the present invention provides a pharmaceutical formulation comprising: a therapeutically effective amount of an IRM compound and a pharmaceutically acceptable vehicle including an oleic acid component, wherein the oleic acid component has a peroxide value no greater than 5.

In another aspect, the present invention provides a pharmaceutical formulation comprising: a therapeutically effective amount of an IRM compound and a pharmaceutically acceptable vehicle including an oleic acid component, wherein the oleic acid component is at least 80% oleic acid.

The present invention also provides methods.

In one aspect, the present invention provides a method of stabilizing a pharmaceutical formulation comprising a therapeutically effective amount of an immune response modifier (IRM) compound and oleic acid by using an oleic acid component that is substantially free of polar impurities.

In one aspect, the present invention provides a method of stabilizing a pharmaceutical formulation comprising a therapeutically effective amount of an IRM compound and oleic acid by using an oleic acid component with a peroxide value no greater than 5.

In one aspect, the present invention provides a method of stabilizing a pharmaceutical formulation comprising a therapeutically effective amount of an IRM compound and oleic acid by using an oleic acid component that is at least 80% oleic acid.

In another aspect, the present invention provides methods for treating disease, including but not limited to the group comprising actinic keratosis, basal cell carcinoma, genital warts, peri-anal warts, malignant melanoma, and molloscum contagiosum. In another aspect, the present invention provides methods to induce cytokine biosynthesis. In another aspect, the present invention provides methods to induce interferon biosynthesis.

A number of additional embodiments can be described as follows:

1. A pharmaceutical formulation comprising:

a therapeutically effective amount of an immune response modifier (IRM) compound selected from the group consisting of imidazoquinoline amines, tetrahydroimidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazoloquinoline amines, thiazoloquinoline amines, oxazolopyridine amines, thiazolopyridine amines, oxazolonaphthyridine amines, thiazolonaphthyridine amines, 1H-imidazo dimers fused to pyridine amines, quinoline amines, tetrahydroquinoline amines, naphthyridine amines, or tetrahydronaphthyridine amines, and combinations thereof; and

a pharmaceutically acceptable vehicle including an oleic acid component, wherein the formulation is substantially free of polar impurities introduced by the oleic acid component.

2. A pharmaceutical formulation comprising:

a therapeutically effective amount of an IRM compound selected from the group consisting of imidazoquinoline amines, tetrahydroimidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazoloquinoline amines, thiazoloquinoline amines, oxazolopyridine amines, thiazolopyridine amines, oxazolonaphthyridine amines, thiazolonaphthyridine amines, 1H-imidazo dimers fused to pyridine amines, quinoline amines, tetrahydroquinoline amines, naphthyridine amines, or tetrahydronaphthyridine amines, and combinations thereof; and

a pharmaceutically acceptable vehicle including an oleic acid component, wherein the oleic acid component has a peroxide value no greater than 5.

3. A pharmaceutical formulation comprising:

a therapeutically effective amount of an IRM compound selected from the group consisting of imidazoquinoline amines, tetrahydroimidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazoloquinoline amines, thiazoloquinoline amines, oxazolopyridine amines, thiazolopyridine amines, oxazolonaphthyridine amines, thiazolonaphthyridine amines, 1H-imidazo dimers fused to pyridine amines, quinoline amines, tetrahydroquinoline amines, naphthyridine amines, or tetrahydronaphthyridine amines, and combinations thereof; and

a pharmaceutically acceptable vehicle including an oleic acid component, wherein the oleic acid component is at least 80% oleic acid.

4. A formulation as in any one of the preceding embodiments wherein the IRM compound is selected from the group consisting of amide substituted imidazoquinoline amines, sulfonamide substituted imidazoquinoline amines, urea substituted imidazoquinoline amines, aryl ether substituted imidazoquinoline amines, heterocyclic ether substituted imidazoquinoline amines, amido ether substituted imidazoquinoline amines, sulfonamido ether substituted imidazoquinoline amines, urea substituted imidazoquinoline ethers, thioether substituted imidazoquinoline amines, 6-, 7-, 8-, or 9-aryl, heteroaryl, aryloxy or arylalkyleneoxy substituted imidazoquinoline amines, imidazoquinoline diamines, amide substituted tetrahydroimidazoquinoline amines, sulfonamide substituted tetrahydroimidazoquinoline amines, urea substituted tetrahydroimidazoquinoline amines, aryl ether substituted tetrahydroimidazoquinoline amines, heterocyclic ether substituted tetrahydroimidazoquinoline amines, amido ether substituted tetrahydroimidazoquinoline amines, sulfonamido ether substituted tetrahydroimidazoquinoline amines, urea substituted tetrahydroimidazoquinoline ethers, thioether substituted tetrahydroimidazoquinoline amines, tetrahydroimidazoquinoline diamines, amide substituted imidazopyridine amines, sulfonamide substituted imidazopyridine amines, urea substituted imidazopyridine amines, aryl ether substituted imidazopyridine amines, heterocyclic ether substituted imidazopyridine amines, amido ether substituted imidazopyridine amines, sulfonamido ether substituted imidazopyridine amines, urea substituted imidazopyridine ethers, thioether substituted imidazopyridine amines, and combinations thereof.

5. A formulation as in any one of embodiments 1 through 3 wherein the IRM compound is an imidazonaphthyridine amine.

6. A formulation as in any one of embodiments 1 through 3 and 5 wherein the IRM compound is 2-methyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine.

7. A formulation as in any one of embodiments 1 through 3 wherein the IRM compound is 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine.

8. A formulation as in any one of the preceding embodiments wherein the IRM compound is present in an amount of at least 3% by weight, based on the total weight of the formulation.

9. A formulation as in any one of the preceding embodiments wherein the IRM compound is present in an amount of at least 5% by weight, based on the total weight of the formulation.

10. A formulation as in any one of the preceding embodiments wherein the oleic acid component is present in an amount of at least 15% by weight based on the total weight of the formulation.

11. A formulation as in any one of the preceding embodiments wherein the oleic acid component is present in an amount of at least 20% by weight based on the total weight of the formulation.

12. A formulation as in any one of the preceding embodiments wherein the oleic acid component is present in an amount of at least 25% by weight based on the total weight of the formulation.

13. A formulation as in any one of the preceding embodiments wherein the oleic acid component has been purified by chromatography prior to use in the formulation.

14. A formulation as in any one of the preceding embodiments wherein the oleic acid component is plant-derived.

15. A formulation as in any one of the preceding embodiments wherein the formulation includes at least one fatty acid other than oleic acid or isostearic acid.

16. A formulation as in any one of the preceding embodiments wherein the formulation includes less than 3% isostearic acid by weight based on the total weight of the formulation.

17. A formulation as in any one of the preceding embodiments wherein the formulation further comprises an antioxidant.

18. A formulation as in any one of the preceding embodiments further comprising an antioxidant, wherein the antioxidant is butylated hydroxyl toluene or butylated hydroxyanisole.

19. A formulation of any one of the preceding embodiments further comprising water.

20. A formulation of any one of the preceding embodiments further comprising a preservative system.

21. A formulation of any one of the preceding embodiments further comprising an emulsifier.

22. A method of stabilizing a pharmaceutical formulation comprising a therapeutically effective amount of an immune response modifier (IRM) compound selected from the group consisting of imidazoquinoline amines, tetrahydroimidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazoloquinoline amines, thiazoloquinoline amines, oxazolopyridine amines, thiazolopyridine amines, oxazolonaphthyridine amines, thiazolonaphthyridine amines, 1H-imidazo dimers fused to pyridine amines, quinoline amines, tetrahydroquinoline amines, naphthyridine amines, or tetrahydronaphthyridine amines, and combinations thereof; and oleic acid by using an oleic acid component that is substantially free of polar impurities.

23. A method of stabilizing a pharmaceutical formulation comprising a therapeutically effective amount of an IRM compound selected from the group consisting of imidazoquinoline amines, tetrahydroimidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazoloquinoline amines, thiazoloquinoline amines, oxazolopyridine amines, thiazolopyridine amines, oxazolonaphthyridine amines, thiazolonaphthyridine amines, 1H-imidazo dimers fused to pyridine amines, quinoline amines, tetrahydroquinoline amines, naphthyridine amines, or tetrahydronaphthyridine amines, and combinations thereof; and oleic acid by using an oleic acid component with a peroxide value no greater than 5.

24. A method of stabilizing a pharmaceutical formulation comprising a therapeutically effective amount of an IRM compound selected from the group consisting of imidazoquinoline amines, tetrahydroimidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazoloquinoline amines, thiazoloquinoline amines, oxazolopyridine amines, thiazolopyridine amines, oxazolonaphthyridine amines, thiazolonaphthyridine amines, 1H-imidazo dimers fused to pyridine amines, quinoline amines, tetrahydroquinoline amines, naphthyridine amines, or tetrahydronaphthyridine amines, and combinations thereof; and oleic acid by using an oleic acid component that is at least 80% oleic acid.

25. The method as in any one of embodiments 22 through 24 wherein the IRM compound is selected from the group consisting of: amide substituted imidazoquinoline amines, sulfonamide substituted imidazoquinoline amines, urea substituted imidazoquinoline amines, aryl ether substituted imidazoquinoline amines, heterocyclic ether substituted imidazoquinoline amines, amido ether substituted imidazoquinoline amines, sulfonamido ether substituted imidazoquinoline amines, urea substituted imidazoquinoline ethers, thioether substituted imidazoquinoline amines, 6-, 7-, 8-, or 9-aryl, heteroaryl, aryloxy, or arylalkyleneoxy substituted imidazoquinoline amines, imidazoquinoline diamines, amide substituted tetrahydroimidazoquinoline amines, sulfonamide substituted tetrahydroimidazoquinoline amines, urea substituted tetrahydroimidazoquinoline amines, aryl ether substituted tetrahydroimidazoquinoline amines, heterocyclic ether substituted tetrahydroimidazoquinoline amines, amido ether substituted tetrahydroimidazoquinoline amines, sulfonamido ether substituted tetrahydroimidazoquinoline amines, urea substituted tetrahydroimidazoquinoline ethers, thioether substituted tetrahydroimidazoquinoline amines, tetrahydroimidazoquinoline diamines, amide substituted imidazopyridine amines, sulfonamide substituted imidazopyridine amines, urea substituted imidazopyridine amines, aryl ether substituted imidazopyridine amines, heterocyclic ether substituted imidazopyridine amines, amido ether substituted imidazopyridine amines, sulfonamido ether substituted imidazopyridine amines, urea substituted imidazopyridine ethers, thioether substituted imidazopyridine amines, and combinations thereof.

26. The method as in any one of embodiments 22 through 24 wherein the IRM compound is an imidazonaphthyridine amine.

27. The method as in any one of embodiments 22 through 24 and 26 wherein the IRM compound is 2-methyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine.

28. The method as in any one of embodiments 22 through 24 wherein the IRM compound is 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine.

29. A method of treating actinic keratosis, the method comprising applying a formulation of any one of embodiments 1 through 21 to the skin of a subject.

30. A method of treating basal cell carcinoma, the method comprising applying a formulation of any one of embodiments 1 through 21 to the skin of a subject.

31. A method of treating genital warts, the method comprising applying a formulation of any one of embodiments 1 through 21 to the skin or mucosal surface of a subject.

32. A method of treating peri-anal warts, the method comprising applying a formulation of any one of embodiments 1 through 21 to the skin or mucosal surface of a subject.

33. A method of treating molloscum contagiosum, the method comprising applying a formulation of any one of embodiments 1 through 21 to the skin of a subject.

34. A method of inducing cytokine biosynthesis, the method comprising applying a formulation of any one of embodiments 1 through 21 to the skin or mucosal surface of a subject.

35. A method of inducing interferon biosynthesis, the method comprising applying a formulation of any one of embodiments 1 through 21 to the skin or mucosal surface of a subject.

36. A method of treating malignant melanoma, the method comprising applying a formulation of any one of the preceding embodiments 1 through 21 to the skin of a subject.

The term "substantially free" is used to indicate that the amount present in the composition or formulation is below the level that causes degradation of the active pharmaceutical agent, such that the formulation is unsuitable for pharmaceutical usage, after storage for 4 months at 40° C. at 75% relative humidity. The term can also be used to describe a composition

containing less than 10%, less than 5%, less than 1%, or less than 0.1% by weight of a given substance.

The term "polar impurities" includes, but is not limited to peroxides, aldehydes, ketones, alcohols, metal ions, and/or substances that cause degradation of the active pharmaceutical agent.

The term "oleic acid component" is used to describe a preformulation source or composition of matter containing oleic acid, and may include other fatty acids in addition to oleic acid, including but not limited to: myristic acid, palmitic acid, palmitoleic acid, margaric acid, isostearic acid, stearic acid, linoleic acid, linolenic acid, and other fatty acids, or combinations thereof.

The peroxide value is the number that expresses in milliequivalents of active oxygen the quantity of peroxide contained in 1000 g of the substance as determined by the methods described in the 5th edition of the European Pharmacopoeia, Section 2.5.5.

Unless otherwise indicated, all numbers expressing quantities, ratios, and numerical properties of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about".

All parts, percentages, ratios, etc. herein are by weight unless indicated otherwise.

As used herein, "a" or "an" or "the" are used interchangeably with "at least one" to mean "one or more" of the listed element.

The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments. In several places throughout the application, guidance is provided through lists of examples, which examples can be used in various combinations. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

DETAILED DESCRIPTION

The present invention provides pharmaceutical formulations that include a therapeutically effective amount of an immune response modifier (IRM) compound selected from the group consisting of imidazoquinoline amines, tetrahydroimidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazoloquinoline amines, thiazoloquinoline amines, oxazolopyridine amines, thiazolopyridine amines, oxazolonaphthyridine amines, thiazolonaphthyridine amines, and 1H-imidazo dimers fused to pyridine amines, quinoline amines, tetrahydroquinoline amines, naphthyridine amines, or tetrahydronaphthyridine amines, and oleic acid, wherein the oleic acid component contains a low amount of polar impurities, especially peroxides. Surprisingly, the stability of such formulations is substantially greater than that of similar formulations containing an IRM compound and oleic acid containing conventional oleic acid with higher amounts of polar impurities such as peroxides, even when the oleic acid component is of compendial grade. Furthermore, the instability problem of these formulations is not eliminated by additional antioxidants.

Through utilization of an oleic acid component containing a very low amount of polar impurities, the subsequent formation of impurities in IRM formulations is significantly reduced as compared to other IRM formulations comprising compendial grades of oleic acid after both the initial measurement (i.e., its measurement when initially formulated) and under accelerated conditions (when stored for at least 4 months at 40° C. and 75% relative humidity), resulting in an increased formulation shelf life.

For certain embodiments, the formulation comprises an IRM compound and a pharmaceutically acceptable vehicle including an oleic acid component wherein the formulation is substantially free of polar impurities introduced by the oleic acid component. For certain embodiments, the formulation comprises an IRM compound and a pharmaceutically acceptable vehicle including an oleic acid component, wherein the oleic acid component has a peroxide value no greater than 5. For certain embodiments, the formulation comprises an IRM compound and a pharmaceutically acceptable vehicle including an oleic acid component, wherein the oleic acid component is at least 80% oleic acid.

In certain embodiments, formulations described herein can be in the form of an oil-in-water emulsion such as a cream or a lotion. The oil component of the formulation includes an IRM compound and one or more fatty acids, including oleic acid in an amount sufficient to solubilize the IRM compound. Optionally, a cream or lotion of the invention can contain emollients, antioxidants, emulsifiers, viscosity enhancing agents, and/or preservatives. Such components, as well as all others of the formulations described herein, are preferably pharmaceutically acceptable.

Immune Response Modifying Compounds

Formulations of the invention include an IRM compound. Such compounds include, for example, imidazoquinoline amines including, but not limited to, substituted imidazoquinoline amines such as, for example, amide substituted imidazoquinoline amines, sulfonamide substituted imidazoquinoline amines, urea substituted imidazoquinoline amines, aryl ether substituted imidazoquinoline amines, heterocyclic ether substituted imidazoquinoline amines, amido ether substituted imidazoquinoline amines, sulfonamido ether substituted imidazoquinoline amines, urea substituted imidazoquinoline ethers, thioether substituted imidazoquinoline amines, 6-, 7-, 8-, or 9-aryl, heteroaryl, aryloxy or arylalkyleneoxy substituted imidazoquinoline amines, and imidazoquinoline diamines; tetrahydroimidazoquinoline amines including, but not limited to, amide substituted tetrahydroimidazoquinoline amines, sulfonamide substituted tetrahydroimidazoquinoline amines, urea substituted tetrahydroimidazoquinoline amines, aryl ether substituted tetrahydroimidazoquinoline amines, heterocyclic ether substituted tetrahydroimidazoquinoline amines, amido ether substituted tetrahydroimidazoquinoline amines, sulfonamido ether substituted tetrahydroimidazoquinoline amines, urea substituted tetrahydroimidazoquinoline ethers, thioether substituted tetrahydroimidazoquinoline amines, and tetrahydroquinoline diamines; imidazopyridine amines including, but not limited to, amide substituted imidazopyridine amines, sulfonamide substituted imidazopyridine amines, urea substituted imidazopyridine amines, aryl ether substituted imidazopyridine amines, heterocyclic ether substituted imidazopyridine amines, amido ether substituted imidazopyridine amines, sulfonamido ether substituted imidazopyridine amines, urea substituted imidazopyridine ethers, and thioether substituted imidazopyridine amines; 1,2-bridged imidazoquinoline amines; 6,7-fused cycloalkylimidazopyridine amines; imidazonaphthyridine amines; tetrahydroimidazonaphthyridine amines; oxazoloquinoline amines; thiazoloquinoline amines; oxazolopyridine amines; thiazolopyridine amines; oxazolonaphthyridine amines; thiazolonaphthyridine amines; and 1H-imidazo dimers fused to pyridine

amines, quinoline amines, tetrahydroquinoline amines, naphthyridine amines, or tetrahydronaphthyridine amines.

These immune response modifier compounds are disclosed in, e.g., U.S. Pat. Nos. 4,689,338, 4,929,624; 5,266,575; 5,268,376; 5,346,905; 5,352,784; 5,389,640; 5,446,153; 5,482,936; 5,756,747; 6,110,929; 6,194,425; 6,331,539; 6,376,669; 6,451,810; 6,525,064; 6,541,485; 6,545,016; 6,545,017; 6,573,273; 6,656,938; 6,660,735; 6,660,747; 6,664,260; 6,664,264; 6,664,265; 6,667,312; 6,670,372; 6,677,347; 6,677,348; 6,677,349; 6,683,088; 6,756,382; U.S. Patent Publication Nos. 2004/0091491; 2004/0132766; 2004/0147543; and 2004/0176367; and International Patent Application No. PCT/US04/28021 filed on Aug. 27, 2004.

For certain of these embodiments, the IRM compound is an imidazonaphthyridine amine. For certain of these embodiments, the IRM compound is 2-methyl-1-(2-methylpropyl-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine. For certain of these embodiments, the IRM compound is an imidazoquinoline amine. For certain of these embodiments, the IRM compound is 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine (imiquimod). For some embodiments, the IRM may have low solubility in water, for example less than about 1 ug/mL (e.g., 0.79 ug/mL in the case of imiquimod), making them difficult to solubilize in aqueous formulations, and potentially using relatively large amounts of oleic acid in the formulation.

The amount of IRM compound that will be therapeutically effective in a specific situation will depend on such things as the activity of the particular compound, the dosing regimen, the application site, the particular formulation and the condition being treated. As such, it is generally not practical to identify specific administration amounts herein; however, those skilled in the art will be able to determine appropriate therapeutically effective amounts based on the guidance provided herein, information available in the art pertaining to IRM compounds, and routine testing. The term "a therapeutically effective amount" means an amount of the IRM compound sufficient to induce a therapeutic or prophylactic effect, such as cytokine induction, inhibition of TH2 immune response, antiviral or antitumor activity, reduction or elimination of postsurgical scarring, reduction or resolution of actinic keratosis or pre-actinic keratosis lesions, reduction in the recurrence of actinic keratosis, treatment of basal cell carcinoma, genital warts, peri-anal warts, molloscum contagiosum, or protection against uv-induced epidermal neoplasia.

In general, the amount of IRM compound present in a topical formulation of the invention will be an amount effective to treat a targeted condition, to prevent recurrence of the condition, or to promote immunity against the condition. In certain embodiments, the amount or concentration of IRM compound is at least 3% by weight, such as, for example, at least 5%, and at least 10%, by weight based on the total weight of the formulation. In other embodiments, the amount of IRM compound is at most 10% by weight, such as, for example, at most 5%, at most 3%, by weight based on the total weight of the formulation. In certain embodiments, the amount or concentration of IRM compound is at least 0.02% by weight, such as, for example, at least 0.03%, at least 0.10%, and at least 0.30% by weight based on the total weight of the formulation.

Fatty Acids

The topical formulations of the invention include fatty acids. In particular, the topical formulations of the invention contain an oleic acid component. As used herein, the term "fatty acid" means a carboxylic acid, either saturated or unsaturated having 6 to 28 carbon atoms, such as, for example, from 10 to 22 carbon atoms.

The fatty acids, including the oleic acid component, may be present in the formulation in an amount sufficient to solubilize the IRM compound. In certain embodiments, the amount of oleic acid component is at least 0.05% by weight at least 1.0% by weight, at least 3.0% by weight, at least 5.0%, at least 10%, at least 15%, or at least 25%, based on the total weight of the formulation. In certain embodiments, the amount of oleic acid component is at most 40% by weight, at most 30% by weight, at most 15% by weight, or at most 10%, based on the total weight of the formulation.

Compendial grade oleic acid typically contains from 65 to 88 percent (Z)-octadec-9-enoic acid (oleic acid) together with varying amounts of saturated and other unsaturated fatty acids. The composition of fat acids is determined by gas chromatography using the method described in European Pharmacopeia monograph 01/2005:0799.

For certain embodiments, the oleic acid component contains at least 50%, at least 60%, at least 70% or at least 80% oleic acid. For certain embodiments, the oleic acid component contains at least 80% oleic acid.

For certain embodiments, the oleic acid component is substantially free of polar impurities, such as peroxides. For certain embodiments, the oleic acid component contains less than 10%, less than 5%, less than 1%, or less than 0.1% by weight of polar impurities. For certain embodiments, the oleic acid component has a peroxide value less than 10. For certain embodiments, the oleic acid component has a peroxide value less than 5.

For certain embodiments, the oleic acid component comprises SUPER REFINED Oleic Acid NF, available from Croda Inc., Edison, N.J., USA.

For certain embodiments, the topical formulations of the invention can include fatty acids in addition to those included in the oleic acid component. For example, certain embodiments can include isostearic acid. In some embodiments, the total amount of fatty acids, including those in the oleic acid component, is at least 0.05% by weight, at least 1.0% by weight, at least 3.0% by weight, at least 5.0%, at least 10%, at least 15%, or at least 25%, based on the total weight of the formulation. In certain embodiments, the total amount of fatty acids, including those in the oleic acid component, is at most 40% by weight, at most 30% by weight, at most 15% by weight, or at most 10%, based on the total weight of the formulation.

Antioxidants

For certain embodiments, the topical formulations of the invention can include an antioxidant.

Suitable antioxidants are those that are pharmaceutically acceptable and described in the International Cosmetic Ingredient Dictionary and Handbook, Ninth Edition, Volume 4, 2002, and in the USP NF 2004: The United States Pharmacopeia, 27th Revision and The National Formulary, 22nd Edition.

Examples of suitable antioxidants include ascorbic acid (D and/or L enantiomers), ascorbyl palmitate (D and/or L enantiomers), butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), cysteine (D and/or L enantiomers), propyl gallate, sodium formaldehyde sulfoxylate, sodium thiosulfate, and tocopherol.

For certain embodiments, the antioxidant is selected from the group comprising aromatic hydroxy groups capable of hydrogen atom donation. Examples of such antioxidants include BHA, BHT, propyl gallate, and tocopherol.

For certain embodiments, the antioxidant is selected from the group consisting of BHA, BHT, and combinations thereof. For certain embodiments, the antioxidant is BHA.

Preservative System

The formulation often will include a preservative system. The preservative system includes one or more compounds that inhibit microbial growth (e.g., fungal and bacterial growth) within the formulation (for example, during manufacturing and use). The preservative system will generally include at least one preservative compound, such as, for example, methylparaben, ethylparaben, propylparaben, butylparaben, benzyl alcohol, phenoxyethanol, and sorbic acid or derivatives of sorbic acid such as esters and salts. Various combinations of these compounds can be included in the preservative system. In some embodiments of the invention, the preservative system includes methylparaben, propylparaben and benzyl alcohol.

In some embodiments of the invention, the preservative compound is present in an amount of at least 0.01% by weight, such as for example, at least 0.02%, at least 0.03%, at least 0.04%, and at least 0.05%, by weight based on the total weight of the formulation. In other embodiments of the invention the preservative compound is present in an amount of at most 3%, such as for example, at most 2.5%, at most 2.0%, at most 1.0%, at most 0.5%, at most 0.4%, at most 0.3%, and at most 0.2%, by weight based on the total weight of the formulation.

Emollients

The topical formulations of the invention may also include at least one emollient. Examples of useful emollients include but are not limited to long chain alcohols, for example, cetyl alcohol, stearyl alcohol, cetearyl alcohol; fatty acid esters, for example, isopropyl mysristate, isopropyl palmitate, diisopropyl dimer dilinoleate; medium-chain (e.g., 8 to 14 carbon atoms) triglycerides, for example, caprylic/capric triglyceride, cetyl esters; hydrocarbons of 8 or more carbon atoms, for example, light mineral oil, white petrolatum; and waxes, for example, beeswax. Various combinations of such emollients can be used if desired.

In certain embodiments, the amount of the emollient is at least 1.0% by weight, at least 3.0% by weight, at least 5.0% by weight, or at least 10% by weight, based on the total weight of the formulation. In certain embodiments, the amount of emollient is at most 30% by weight, at most 15% by weight, or at most 10% by weight, based on the total weight of the formulation.

Formulations intended for dermal or topical use typically have amounts of an oil phase and an emollient sufficient to provide desirable qualities such as spreadability and feel.

Viscosity Enhancing Agent

The formulations of the present invention can also comprise a viscosity-enhancing agent. Examples of suitable viscosity enhancing agents include long chain alcohols, for example, cetyl alcohol, stearyl alcohol, cetearyl alcohol; cellulose ethers such as hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, and carboxymethylcellulose; polysaccharide gums such as xanthan gum; and homopolymers and copolymers of acrylic acid crosslinked with allyl sucrose or allyl pentaerythriol such as those polymers designated as carbomers in the United States Pharmacopoeia. Suitable carbomers include, for example, those available as CARBOPOL 934P, CARBOPOL 971P, CARBOPOL 940, CARBOPOL 974P, CARBOPOL 980, and PEMULEN TR-1 (USP/NF Monograph; Carbomer 1342), all available from Noveon, Cleveland, Ohio.

In certain embodiments, the amount of the viscosity enhancing agent, when used, is at least 0.1% by weight, at least 0.2% by weight, at least 0.5% by weight, at least 0.6% by weight, at least 0.7% by weight, at least 0.9% by weight, or at least 1.0% by weight, based on the total weight of the formulation. In certain embodiments, the amount of the viscosity-enhancing agent, when used, is at most 10% by weight, at most 5.0% by weight, at most 3.0% by weight, at most 2.0% by weight, or at most 1.5% by weight, based on the total weight of the formulation.

Emulsifier

The formulations of the invention can additionally comprise an emulsifier. Suitable emulsifiers include non-ionic surfactants such as, for example, polysorbate 60, sorbitan monostearate, polyglyceryl-4 oleate, polyoxyethylene(4) lauryl ether, etc. In certain embodiments, the emulsifier is chosen from poloxamers (e.g., PLURONIC F68, also known as POLOXAMER 188, a poly(ethylene glycol)-block-poly (propylene glycol)-block-poly(ethylene glycol), available from BASF, Ludwigshafen, Germany) and sorbitan trioleate (e.g., SPAN 85 available from Uniqema, New Castle, Del.).

If included, the emulsifier is generally present in an amount of 0.1% to 10% by weight of total formulation weight, for example, from 0.5% to 5.0% by weight, and from 0.75% to 4.0% by weight. In certain embodiments, the amount of the emulsifier, if used, is present in an amount of at least 0.1% by weight, at least 0.5% by weight, at least 0.75% by weight, at least 1.0% by weight, at least 2.5% by weight, at least 3.5% by weight, at least 4.0% by weight, or at least 5.0% by weight, based on the total weight of the formulation. In certain embodiments, the amount of the emulsifier, if used, is present in an amount of at most 10% by weight, at most 5.0% by weight, or at most 3.5% by weight, based on the total weight of the formulation.

Some formulations of the invention are oil-in-water emulsions. The water used in these formulations is typically purified water

Optionally, a formulation of the invention can contain additional pharmaceutically acceptable excipients such as humectants, such as for example, glycerin; chelating agents, such as for example, ethylenediaminetetraacetic acid; and pH adjusting agents, such as for example, potassium hydroxide or sodium hydroxide.

In some instances, a single ingredient can perform more than one function in a formulation. For example, cetyl alcohol can serve as both an emollient and a viscosity enhancer.

Illustrative Formulation

In one embodiment of the present invention, a pharmaceutical formulation includes:

5% by weight of 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine;
28% by weight SUPER REFINED oleic acid;
2.2% by weight cetyl alcohol;
3.1% by weight stearyl alcohol;
3% by weight petrolatum;
3.4% by weight polysorbate 60;
0.6% by weight sorbitan monostearate;
2% by weight glycerin;
0.2% by weight methyl hydroxybenzoate;
0.02% by weight propyl hydroxybenzoate;
0.5% by weight xanthan gum;
2% by weight of benzyl alcohol; and
49.98% by weight water;

Methods of Application

Formulations according to the present invention can be applied to any suitable location, for example topically to dermal and/or mucosal surfaces. In the case of dermal application, for example, depending on the IRM compound concentration, formulation composition, and dermal surface, the therapeutic effect of the IRM compound may extend only to the superficial layers of the dermal surface or to tissues below the dermal surface. Thus, another aspect of the present invention is directed to a method for the treatment of a dermal and/or mucosal associated condition comprising applying to skin one of the foregoing formulations. As used herein, a "dermal and/or mucosal associated condition" means an inflammatory, infectious, neoplastic or other condition that involves a dermal and/or mucosal surface or that is in sufficient proximity to a dermal and/or mucosal surface to be affected by a therapeutic agent topically applied to the surface. Examples of a dermal and/or mucosal associated condition include warts, atopic dermatitis, postsurgical scars, lesions caused by a herpes virus, and epidermal neoplasias, such as for example actinic keratosis, pre-actinic keratosis lesions, malignant melanomas, basal cell carcinoma, and squamous cell carcinoma.

In one embodiment, the formulations can be applied to the surface of skin for treatment of actinic keratosis (AK). Actinic keratosis are premalignant lesions considered biologically to be either carcinoma in-situ or squamous intraepidermal neoplasia. AK is the most frequent epidermal tumor and is induced by ultraviolet (UV) radiation, typically from sunlight. Because of its precancerous nature, AK may be considered the most important manifestation of sun-induced skin damage.

In some embodiments, the above-described formulations are particularly advantageous for dermal and/or mucosal application for a period of time sufficient to obtain a desired therapeutic effect without undesired systemic absorption of the IRM compound.

Examples

The following Examples are provided to further describe various formulations and methods according to the invention. The examples, however, are not intended to limit the formulations and methods within the spirit and scope of the invention.

Test Method

A reversed phase high performance liquid chromatography (HPLC) method was used to determine the amount of impurities in cream formulations containing oleic acid.

HPLC parameters: Analytical column: ZORBAX RX C8, 5 micron particle, 15.0×0.46 cm, (available from Agilent Technologies, Wilmington, Del., USA); Detector: UV at 308 nm; Mobile phase: gradient mixture of aqueous ammonium phosphate buffer (prepared by combining 5.1 mL of orthophosphoric acid with 985 mL of water and then adjusting to pH 2.5 with concentrated ammonium hydroxide) and acetonitrile; Gradient: start run at 10% acetonitrile, zero initial hold time, then linear gradient to 70% acetonitrile over 15 minutes, zero final hold time; Flow rate: 2.0 mL/minute; Injection volume: 200 μL; Run time: 15 minutes.

Sample solution: A portion (about 300 mg) of the cream formulation was accurately weighed into a volumetric flask (100 mL). Diluent (50 to 60 mL, prepared by combining 250 parts of acetonitrile, 740 parts of water and 10 parts of hydrochloric acid, all parts by volume) was added to the flask. The flask was vortexed until the cream was completely dispersed and then sonicated for a minimum of 5 minutes. The solution was allowed to cool to ambient temperature and then diluted to volume with diluent and mixed. A portion of the solution was filtered using a syringe equipped with a 0.45 micron polypropylene or polytetrafluoroethylene filter to provide the sample solution.

Preparation of Cream Formulations

The cream formulations in Table 1 below were prepared using the following method.

Water phase preparation: A paraben premix was prepared by combining methyl hydroxybenzoate (methylparaben), propyl hydroxybenzoate (propylparaben), and water; heating the mixture with stirring until the parabens were dissolved; and then allowing the resulting solution to cool to ambient temperature. Glycerin was added to the premix and the mixture was heated to 55±5° C. Xanthan gum was slowly added with mixing. Mixing with heating was continued until the xanthan gum was dispersed.

Oil phase preparation: An imiquimod/oleic acid premix was prepared by combining imiquimod and the oleic acid and then stirring at ambient temperature overnight. Petrolatum, cetyl alcohol, stearyl alcohol, polysorbate 60, sorbitan monostearate, and butylated hydroxyanisole (BHA), if included, were added to the premix. The oil phase was then heated with stirring to 55±5° C. Benzyl alcohol was added to the oil phase just prior to phase combination.

Phase combination: Both phases were removed from their heat source. The aqueous phase was added to the oil phase and the emulsion was homogenized at high speed for at least 5 minutes. The cream was placed in an ice/water bath while homogenizing and homogenization was continued until the temperature of the cream was 35° C., The homogenizer speed was reduced and homogenization was continued until the temperature of the cream was 25° C.

Table 1 summarizes creams A-D in percentage weight-by-weight basis. The formulations were packaged in glass containers.

TABLE 1

Ingredient	A	B	C	D
[1]Imiquimod	5	5	5	5
[2]Oleic acid, NF	28	28	—	—
[3]SUPER REFINED oleic acid, NF	—	—	28	28
Cetyl alcohol	2.2	2.2	2.2	2.2
Stearyl alcohol	3.1	3.1	3.1	3.1
Petrolatum	3	3	3	3
Polysorbate 60	3.4	3.4	3.4	3.4
Sorbitan monostearate	0.6	0.6	0.6	0.6
Benzyl alcohol	2	2	2	2
BHA	—	1	—	1
Glycerin	2	2	2	2
Methylparaben	0.2	0.2	0.2	0.2
Propylparaben	0.02	0.02	0.02	0.02
Xanthan gum	0.5	0.5	0.5	0.5
Water	qs 100	qs 100	qs 100	qs 100

[1]1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine
[2]J. T. Baker, a division of Mallinckrodt Baker, Inc, Phillipsburg, NJ, USA
[3]Croda, Inc, Edison, NJ, USA

One set of containers was stored at ambient conditions; the samples used to determine initial values came from these containers. The remaining containers were stored in a constant temperature and humidity chamber at 40° C. at 75% relative humidity. At selected time points, containers were removed from the chamber and then stored at ambient con-

ditions until analyzed. Samples were analyzed using the test method described above for impurities. At the 2, 4, and 6 month time points samples were taken from both the top and the bottom of the containers. The results are shown in Table 2 below where each value is the result of a single determination. Values are not normalized for weight loss that may have occurred during storage.

TABLE 2

	Impurities (% wt/wt)			
Timepoint	A	B	C	D
[1]Initial - top	0.09	0.08	0.02	0.03
[2]2 months - top	0.25	0.32	0.07	0.09
[2]2 months - bottom	0.33	0.30	0.04	0.15
[3]4 months - top	0.42	0.76	0.18	0.15
[3]4 months - bottom	0.46	0.56	0.04	0.29
[4]6 months - top	0.81	0.30	0.07	0.14
[4]6 months - bottom	0.49	0.29	0.04	0.07

[1]Creams A, B, C, and D were analyzed 16 days, 15 days, 14 days, and 15 days respectively after they were prepared.
[2]All samples were analyzed 10 days after the containers were removed from the constant temperature and humidity chamber.
[3]All samples were analyzed 12 days after the containers were removed from the constant temperature and humidity chamber.
[4]All samples were analyzed 7 days after the containers were removed from the constant temperature and humidity chamber.

The complete disclosures of the patents, patent documents and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. In case of conflict, the present specification, including definitions, shall control. Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. Illustrative embodiments and examples are provided as examples only and are not intended to limit the scope of the present invention. The scope of the invention is limited only by the claims set forth as follows.

What is claimed is:

1. A pharmaceutical cream for topical application to a dermal or mucosal surface for topical delivery of 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine (imiquimod), said pharmaceutical cream comprising:

a therapeutically effective amount of imiquimod; and

a pharmaceutically acceptable vehicle including an oleic acid component,

wherein the oleic acid component at or prior to formulation of said pharmaceutical cream contains at least about 80% oleic acid by weight as a fatty acid, and

wherein the oleic acid component at or prior to formulation of said pharmaceutical cream has a peroxide value of less than about 5 milliequivalents of oxygen per kilogram and contains less than about 1% by weight polar impurities, and

wherein said pharmaceutical cream contains imiquimod-related impurities in an amount of no more than about 0.03% wt./wt. after storage of said pharmaceutical cream at ambient conditions for about 15 days, when absorbance of said pharmaceutical cream is analyzed at about 308 nm using a UV detector.

2. The pharmaceutical cream of claim 1, wherein said pharmaceutical cream contains imiquimod-related impurities in an amount of no more than about 0.02% wt./wt. after storage of said pharmaceutical cream at ambient conditions for about 15 days, when absorbance of said pharmaceutical cream is analyzed at about 308 nm using a UV detector.

3. The pharmaceutical cream of claim 1, wherein said pharmaceutical cream further comprises an antioxidant selected from a group of antioxidants consisting of butylated hydroxyl toluene and butylated hydroxyanisole.

4. The pharmaceutical formulation of claim 1, wherein the imiquimod is present in an amount of no more than about 10% by weight based on the total weight of said pharmaceutical cream and wherein the oleic acid component is present in an amount of no more than about 40% by weight based on the total weight of said pharmaceutical cream.

5. The pharmaceutical cream of claim 1, wherein the imiquimod is present in an amount of about 5% by weight based on the total weight of said pharmaceutical cream and wherein the oleic acid component is present in an amount of no more than about 30% by weight based on the total weight of said pharmaceutical cream.

6. The pharmaceutical cream of claim 1, wherein the imiquimod is present in an amount of about 5% by weight based on the total weight of said pharmaceutical cream and wherein the oleic acid component is present in an amount of about 28% by weight based on the total weight of said cream formulation.

7. A pharmaceutical cream for topical application to a dermal or mucosal surface for topical delivery of 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine (imiquimod), said pharmaceutical cream comprising:

a therapeutically effective amount of imiquimod; and

a pharmaceutically acceptable vehicle including an oleic acid component,

wherein the oleic acid component at or prior to formulation of said pharmaceutical cream contains at least about 80% oleic acid by weight as a fatty acid, and

wherein the oleic acid component at or prior to formulation of said pharmaceutical cream has a peroxide value of less than about 5 millicquivalents of oxygen per kilogram and contains less than about 1% by weight polar impurities, and

wherein said pharmaceutical cream contains imiquimod-related impurities in an amount of no more than about 0.15% wt./wt. after storage of said pharmaceutical cream for at least about 2 months at about 40° C. and about 75% humidity, when absorbance of said pharmaceutical cream is analyzed at about 308 nm using a UV detector.

8. The pharmaceutical cream of claim 7, wherein said pharmaceutical cream contains imiquimod-related impurities in an amount of no more than about 0.07% wt./wt. after storage of said pharmaceutical cream for at least about 2 months at about 40° C. and about 75% humidity, when absorbance of said pharmaceutical cream is analyzed at about 308 nm using a UV detector.

9. The pharmaceutical cream of claim 7, wherein said pharmaceutical cream further comprises an antioxidant selected from a group of antioxidants consisting of butylated hydroxyl toluene and butylated hydroxyanisole.

10. The pharmaceutical cream of claim 7, wherein the imiquimod is present in an amount of no more than about 10% by weight based on the total weight of said pharmaceutical cream and wherein the oleic acid component is present in an amount of no more than about 40% by weight based on the total weight of said pharmaceutical cream.

11. The pharmaceutical cream of claim 7, wherein the imiquimod is present in an amount of about 5% by weight based on the total weight of said pharmaceutical cream and wherein the oleic acid component is present in an amount of no more than about 30% by weight based on the total weight of said pharmaceutical cream.

12. The pharmaceutical cream of claim 7, wherein the imiquimod is present in an amount of about 5% by weight

based on the total weight of said pharmaceutical cream and wherein the oleic acid component is present in an amount of about 28% by weight based on the total weight of said pharmaceutical cream.

13. A pharmaceutical cream for topical or application to a dermal or mucosal surface to deliver 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine (imiquimod) to treat a dermal and/or mucosal associated condition, said pharmaceutical cream having enhanced imiquimod stability and comprising:

a therapeutically effective amount of imiquimod; and

a pharmaceutically acceptable vehicle including an oleic acid component,

wherein the oleic acid component at or prior to formulation of said pharmaceutical cream contains at least about 80% oleic acid by weight as a fatty acid, and

wherein the oleic acid component at or prior to formulation of said pharmaceutical cream has a peroxide value of less than about 5 milliequivalents of oxygen per kilogram and contains less than about 1% by weight polar impurities, and

wherein said pharmaceutical cream contains imiquimod-related impurities in an amount of no more than about 0.29% wt./wt. after storage for at least about 4 months at about 40° C. and about 75% humidity, when absorbance of said pharmaceutical cream is analyzed at about 308 nm using a UV detector.

14. The pharmaceutical cream of claim 13, wherein said pharmaceutical cream contains imiquimod-related impurities in an amount of no more than about 0.15% wt./wt. after storage of said pharmaceutical cream for at least about 4 months at about 40° C. and about 75% humidity, when absorbance of said pharmaceutical cream is analyzed at about 308 nm using a UV detector.

15. The pharmaceutical cream of claim 13, wherein said pharmaceutical cream further comprises an antioxidant selected from a group of antioxidants consisting of butylated hydroxyl toluene and butylated hydroxyanisole.

16. The pharmaceutical cream of claim 13, wherein the imiquimod is present in an amount of no more than about 10% by weight based on the total weight of said pharmaceutical cream and wherein the oleic acid component is present in an amount of no more than about 40% by weight based on the total weight of said pharmaceutical cream.

17. The pharmaceutical formulation of claim 13, wherein the imiquimod is present in an amount of about 5% by weight based on the total weight of said pharmaceutical cream and wherein the oleic acid component is present in an amount of no more than about 30% by weight based on the total weight of said pharmaceutical cream.

18. The pharmaceutical cream of claim 13, wherein the imiquimod is present in an amount of about 5% by weight based on the total weight of said pharmaceutical cream and wherein the oleic acid component is present in an amount of about 28% by weight based on the total weight of said pharmaceutical cream.

19. The pharmaceutical cream of claim 7, wherein said pharmaceutical cream contains imiquimod-related impurities in an amount of (a) no more than about 0.04% wt./wt. after storage of said pharmaceutical cream for at least about 2 months at about 40° C. and about 75% humidity and (b) no more than about 0.04% wt./wt. after storage of said pharmaceutical cream for at least about 4 months at about 40° C. and about 75% humidity, when absorbance of said pharmaceutical cream is analyzed at about 308 nm using a UV detector.

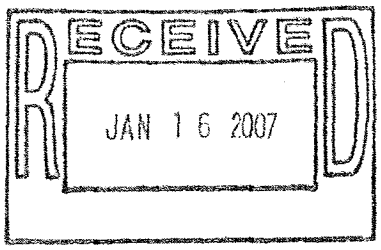
20. The pharmaceutical cream of claim 7, wherein said pharmaceutical cream contains imiquimod-related impurities in an amount of (a) no more than about 0.15% wt./wt. after storage of said pharmaceutical cream for at least about 2 months at about 40° C. and about 75% humidity and (b) no more than about 0.15% wt./wt. after storage of said pharmaceutical cream for at least about 4 months at about 40° C. and about 75% humidity, when absorbance of said pharmaceutical cream is analyzed at about 308 nm using a UV detector.

* * * * *

Part 2

EXHIBIT C

Pharma



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January 10, 2007

Jefferson J. Gregory, Chairman and CEO
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Certified Mail
Return Receipt Requested

Notification of Noninfringement of Patent No. 5,238,944

Dear Mr. Gregory:

To provide notice to 3M and 3M Innovative Properties Company (collectively "3M") as provided by Section 505(j)(2)(B) (ii) of the FD&C Act and 21 C.F.R. § 314.95, herein below is provided a detailed statement of the factual and legal basis for noninfringement of U.S. Patent No. 5,238,944 ("the '944 patent").

I. INTRODUCTION

ALTANA Inc ("ALTANA") has filed with the United States Food and Drug Administration (FDA) in Rockville, Maryland, an Abbreviated New Drug Application (ANDA Number 78-548) pursuant to 21 U.S.C. § 355(j) to obtain approval to market its Imiquimod Cream 5% ("the product"), before the expiration date of the '944 patent on August 24, 2010. The ANDA contains any required bioavailability or bioequivalence data or information.[1]

To the best of ALTANA's knowledge, 3M is the holder of record of the approved application under 21 U.S.C. § 355(b) for the product (NDA 020723) and 3M or its subsidiary, 3M Innovative Properties Company, is the owner of record of U.S. Patent Nos. 5,238,944 and 4,689,338 ("the '338 patent")[2] which have been listed in the FDA Orange Book as covering the product Aldara®. As ALTANA has filed a paragraph III certification with respect to the '338 patent, it will not be further discussed.

ALTANA has also filed with the FDA, pursuant to 21 U.S.C. § 355(j)(A)(vii)(IV), a Paragraph IV Certification stating that, in its opinion and to the best of its knowledge, the claims of the '944 patent will not be infringed by the manufacture, use, sale, offer for sale, importation or offer to import ALTANA's product.

[1] Composition attached as Appendix 3.
[2] Attached as Appendices 1 and 2.

Set forth below is a detailed statement of factual and legal bases of ALTANA's opinion that the '944 patent will not be infringed. Please be advised that ALTANA considers this information to be confidential, is disclosing this information to you solely to comply with 21 U.S.C. § 355(j)(2)(B), and requests that you protect this information from disclosure to third parties by means consistent with your standards for protecting your own confidential information. THIS CONFIDENTIALITY APPLIES TO THIS LETTER, WHICH SHOULD NOT BE ATTACHED TO ANY COMPLAINT OR OTHER PUBLICLY AVAILABLE DOCUMENT.

II. SUMMARY

The claims of the '944 patent all recite that the formulations contain imiquimod and *inter alia* isostearic acid. ALTANA's product does not contain isostearic acid. Amendments and arguments made during the prosecution of the application that issued as the '944 patent cancelling oleic acid from the claims in response to obviousness rejections will estop 3M from arguing that the ALTANA product, containing oleic acid in place of isostearic acid, is the legal equivalent of the formulations of claims 1-13.

Wick et al. (U.S. Patent No. 5,238,944)

A. All of the claims of the '944 patent are directed to, or recite the use of, formulations containing isostearic acid. Claims 1-11 of the '944 patent are directed to imiquimod formulations that contain various amounts of isostearic acid. Thus, claims 1-3 and 6 are directed to a pharmaceutical formulation comprising imiquimod in a vehicle comprising about 3 to about 45 weight percent isostearic acid; about 5 to about 25 weight percent isostearic acid (claim 4); about 3 to about 25 weight percent isostearic acid (claim 5); about 10 percent isostearic acid (claims 7-9); about 25% isostearic acid (claim 10); and about 5 percent isostearic (claim 11).[3] Claims 12-13 are directed to methods of using the formulation of claim 1. Claim 1 is the only independent claim. All of the claims are reproduced below.

> 1. A substantially non-irritating pharmaceutical formulation for topical and/or transdermal administration of the agent 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine [imiquimod], which formulation comprises:
>
> (a) a therapeutically effective amount of 1-isobutyl-1-H-imidazo[4,5-q]quinolin-4-amine; and
>
> (b) a pharmaceutically acceptable vehicle for said 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, which vehicle comprises isostearic acid in an amount of about 3 percent to about 45 percent by weight based on the total weight of said formulation, said formulation being further

[3] Claims 1-11 are directed to formulations. Claims 12-13 are directed to methods of use of the formulations of claim 1, and so contain all of the limitations of claim 1.

characterized in that, when tested according to the hairless mouse skin model the formulation provides a penetration of the agent of at least about 10 percent of the total amount of the agent contained in the formulation in 24 hours.

2. A formulation according to claim 1 wherein said 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine is present in an amount of about 0.5 percent to about 9 percent by weight based on the total weight of said formulation.

3. A formulation according to claim 1 in the form of a cream, comprising an oil phase and a water phase in admixture, said oil phase comprising:

(a) said 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine;

(b) said isostearic acid;

(c) one or more emollients present in a total amount of about 5 percent to about 30 percent by weight based on the total weight of said formulation; and

(d) one or more emulsifiers selected from the group consisting of a nonionic surface active agent and a trivalent cationic emulsifier and present in a total amount of about 2 percent to about 14 percent by weight based on the total weight of said formulation;

said water phase comprising water in an amount of about 45 percent to about 85 percent by weight based on the total weight of said formulation.

4. A formulation according to claim 3 wherein said isostearic acid is present in an amount of about 5 percent to about 25 percent by weight based on the total weight of said formulation.

5. A formulation according to claim 1 in the form of an ointment comprising:

(a) said 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine;

(b) said isostearic acid in an amount of about 3 percent to about 25 percent by weight based on the total weight of said formulation; and

(c) a pharmaceutically acceptable ointment base in an amount of about 60 percent to about 95 percent by weight based on the total weight of said formulation.

6. A formulation according to claim 3 wherein said 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine is present in an amount of about 1 percent to about 5 percent by weight based on the total weight of said formulation.

7. A formulation according to claim 4, comprising about 1 percent of said 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, about 10 percent of

said isostearic acid, about 2 percent benzyl alcohol, about 2.2 percent cetyl alcohol, about 3.1 percent stearyl alcohol, about 2.55 percent polysorbate 60, about 0.45 percent sorbitan monostearate, about 2 percent glycerin, about 0.2 percent methylparaben, about 0.02 percent propylparaben and about 76.48 percent purified water, all percentages being based on the total weight of said formulation.

8. A formulation according to claim 4, comprising about 1 percent of said 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, about 10 percent of said isostearic acid, about 6 percent cetearyl alcohol, about 2.55 percent polysorbate 60, about 0.45 percent sorbitan monostearate, about 2 percent glycerin, about 0.2 percent methylparaben, about 0.02 percent propylparaben and about 77.78 percent purified water, all percentages being based on the total weight of said formulation

9. A formulation according to claim 4, comprising about 1 percent of said 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, about 10 percent of said isostearic acid about 2 percent benzyl alcohol, about 1.7 percent cetyl alcohol, about 2.3 percent stearyl alcohol, about 2.55 percent polysorbate 60, about 0.45 percent sorbitan monostearate, about 2 percent glycerin, about 0.2 percent methylparaben, about 0.02 percent propylparaben and about 77.78 percent purified water, all percentages being based on the total weight of said formulation.

10. A formulation according to claim 4, comprising about 5 percent of said 1-isobutyl-1H-imidazo-[4,5-c]quinolin-4-amine, about 25 percent of said isostearic acid, about 2 percent benzyl alcohol, about 2.2 percent cetyl alcohol, about 3.1 percent stearyl alcohol, about 3 percent petrolatum, about 3.4 percent polysorbate 60, about 0.6 percent sorbitan monostearate, about 2 percent glycerin, about 0.2 percent methylparaben, about 0.02 percent propylparaben and about 53.48 percent purified water, all percentages being based on the total weight of said formulation.

11. A formulation according to claim 4, comprising about 1 percent of said 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, about 5 percent of said isostearic acid, about 15 percent petrolatum, about 12.8 percent light mineral oil, about 8 percent aluminum stearate, about 4 percent cetyl alcohol, about 3 percent polyglyceryl-4 oleate, about 1 percent acetylated lanolin, about 0.063 percent propylparaben, about 1 percent Veegum K, about 0.12 percent methylparaben and about 49.02 percent purified water, all percentages being based on the total weight of said formulation.

12. A method of topical and/or transdermal administration of 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine for treating a viral disease in a mammal, which method comprises

(1) placing a formulation according to claim 1 on the skin of a mammal; and

(2) allowing said formulation to remain in contact with the skin for a sufficient time to permit an effective amount of the 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine to penetrate the skin to achieve the antiviral effect.

13. A method of topical and/or transdermal administration of 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine to induce interferon biosynthesis in a mammal, which method comprises

(1) placing a formulation according to claim 1 on the skin of a mammal; and

(2) allowing said formulation to remain in contact with the skin for a sufficient time to permit an effective amount of 1-isobutyl 1H-imidazo[4,5-c]-quinolin-4-amine to penetrate the skin to induce interferon biosynthesis.

* * *

B. ALTANA's Product Does Not Infringe Any of the Claims of the '944 Patent

In order to determine whether or not a product infringes any of a patent's claims, the claim limitations must be interpreted and their meaning ascertained, as of the date of the invention, e.g., the effective filing date of the application. Schering Corp. v. Amgen, Inc., 222 F.3d 1347 (Fed. Cir. 2000). In determining the meaning of a claim to one of ordinary skill in the art, a court will refer to the claims, the specification, and the prosecution history of the patent. This is referred to as "intrinsic" evidence. Markman v. Westview Instruments, Inc., 52 F.3d 967, 979 (Fed. Cir. 1995) (*en banc*), aff'd 116 S. Ct. 1384 (1996); Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1581-1582 (Fed. Cir. 1996).

The properly interpreted claims are then compared to the accused product or process to see if it infringes any of the patent claims. Infringement is a question of fact and a claim may be infringed either literally or under the doctrine of equivalents. Literal infringement exists when every limitation recited in the claim is found in the accused device (i.e., when the properly construed claim reads on the accused device exactly). SmithKline Diagnostics, Inc. v. Helena Laboratories Corp., 859 F.2d 878 (Fed. Cir. 1988). If there is no literal infringement, infringement under the doctrine of equivalents can be found where the accused product has, at least, an equivalent of every limitation of the claim. Ethicon Endo-Surgery v. U.S. Surgical Corp., 149 F.3d 1309 (Fed. Cir. 1998); Warner-Jenkinson Co. v. Hilton Davis Chem. Co., 117 S.Ct. 1040 (1997) ("Hilton Davis").

As can be seen from the formulation attached as Appendix 3, ALTANA's imiquimod product does not contain isostearic acid, and so does not literally infringe any of the claims of the '944 patent.

The ALTANA product also does not infringe any of the claims of the '944 patent under the doctrine of equivalents. It is well-settled law that the doctrine of equivalents cannot be employed by a patent holder to recapture subject matter given up during prosecution to avoid prior art, whether by amendment of the claims or by arguments presented to the Patent Office. Perkin-Elmer Corp. v. Computervision Corp., 732 F.2d 888 (Fed. Cir. 1984); Pharmacia & Upjohn Co. v. Mylan Pharms., Inc., 170 F.3d 1373 (Fed. Cir. 1999). This is referred to as "prosecution history estoppel."

In Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 122 S.Ct. 1831 (2002), the Supreme Court clarified both the acts during prosecution that would give rise to prosecution history estoppel, and the extent of the estoppel. The Court first held that a narrowing amendment made to satisfy any requirement of the Patent Act gives rise to estoppel: "A patentee who narrows a claim as a condition for obtaining a patent disavows his claim to the broader subject matter." Id. at 1840. The Court then considered the question: "Does the estoppel bar the inventor from asserting infringement against any equivalent to the narrowed element or might some equivalents still infringe?" Id. The Court rejected an absolute bar to application of the doctrine of equivalents to such a narrowed claim, but established a rebuttable presumption that the patentee had generally disclaimed all the territory between the original claim and the amended claim. The patentee can rebut the presumption by explaining why the amendment did not "surrender the particular equivalent in question." Id. at 1842. For example, the patentee might establish that the equivalent was unforseeable when the application was filed, so it could not later have been claimed, or provide some other reason that the equivalent could not reasonably have been expected to have been described in the patent. The patentee can also meet the burden by showing that the rationale underlying the amendment may have "no more than a tangential relation to the equivalent." Id.

A review of the prosecution history of the '944 patent indicates that 3M is estopped from arguing that ALTANA's product is the equivalent of the composition of claims 1-13. Amendments made by the attorney during prosecution that specifically deleted oleic acid from the claims will absolutely estop 3M from arguing the equivalency of ALTANA's product to the claimed composition.

The '944 patent issued out of U.S. patent application Serial No. 07/845,323, filed March 3, 1992. The application was filed with 33 claims. Claim 1 was the only independent claim directed to a formulation or a method-of-use. Claim 27 was a transdermal "patch" claim that is not relevant here. Claims 1-4 are reproduced below:

> 1. A substantially non-irritating pharmaceutical formulation for topical and/or transdermal administration of the agent 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, which formulation comprises:

(a) 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine in an amount of about 0.5 percent to about 9 percent by weight based on the total weight of said formulation; and

(b) a pharmaceutically acceptable vehicle for said 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, which vehicle comprises a fatty acid selected from the group consisting of isostearic acid, oleic acid and a mixture thereof in a total amount of about 3 percent to about 45 percent by weight based on the total weight of said formulation, said formulation being further characterized in that, when tested according to the hairless mouse skin model the formulation provides a penetration of the agent of at least about 10 percent of the total amount of the agent contained in the formulation in 24 hours.

2. A formulation according to Claim 1 wherein said fatty acid is isostearic acid.

3. A formulation according to Claim 1 wherein said fatty acid is oleic acid.

4. A formulation according to Claim 1 wherein said fatty acid is a mixture of isostearic acid and oleic acid.

In the first Office Action, the Examiner withdrew claims 16-31 and rejected claims 1-15 and 32-33 under 35 U.S.C. § 103 as obvious over a combination of four references, including the '338 patent and M. Mahjour et al. (U.S. Patent No. 4,908,389). In response, the 3M attorney canceled claims 16-31 in an Amendment dated August 21, 1992 and submitted an affidavit of Stephen M. Berge that the attorney argued established that oleic acid and isostearic acid "afford better delivery characteristics than palmitic and stearic acid." However, in an Office Action mailed November 13, 1992, the Examiner maintained the rejection, arguing that "[t]he affidavit demonstrates results that would have been expected for the use of oleic acid as a penetration enhancer given the explicit disclosure by Mahjour et al. at column 3, lines 11-13."

In response, the attorney cancelled claims 1-6, 8 and 14-15 and added claims 34-36. Claims 34-38 eventually issued as claims 1-5 of the '944 patent and claim 34 is reproduced below:

34. A substantially non-irritating pharmaceutical formulation for topical and/or transdermal administration of the agent 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, which formulation comprises:

(a) a therapeutically effective amount of 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine; and

(b) a pharmaceutically acceptable vehicle for said 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, which vehicle comprises isostearic acid in an amount of about 3 percent to about 45 percent by weight based on

> the total weight of said formulation, said formulation being further characterized in that, when tested according to the hairless mouse skin model the formulation provides a penetration of the agent of at least about 10 percent of the total amount of the agent contained in the formulation in 24 hours.

The amendments accomplished the deletion of oleic acid from the claims. The attorney stated that "claim 34 represents cancelled claim 1...the claims have been amended so they read only on those compositions that contain isostearic acid; that is, they read only on those compositions for which the Examiner admits unexpected results have been demonstrated...[and] [t]he method claims 32 and 33 contain limitations in addition to those found in the composition claims..." The Examiner then allowed claims 7, 9-13 and 32-38 "(renumbered as 6, 7-11, 12, 13 and 1-5, respectively)."

Since oleic acid was explicitly surrendered when it was cancelled from the claims, the Festo standards for rebuttal of complete surrender of oleic acid do not apply. Therefore, 3M is estopped from asserting that ALTANA's product is equivalent to the claimed compositions, and ALTANA's product will not infringe any of the claims of the patent.

III. CONCLUSION

The foregoing provides a detailed factual and legal basis supporting ALTANA's opinion that the '944 patent will not be infringed, in accord with 21 U.S.C. § 355(j)(2)(B)(ii).

ALTANA reserves the right to supplement this statement with information that may have been discovered in litigation over the same patents or otherwise becomes relevant.

Sincerely,

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United States Patent and Trademark Office

Assignments on the Web > Patent Query

Patent Assignment Abstract of Title

NOTE:Results display only for issued patents and published applications. For pending or abandoned applications please consult USPTO staff.

Total Assignments: 2

Patent #: 5238944 **Issue Dt:** 08/24/1993 **Application #:** 07845323 **Filing Dt:** 03/03/1992

Inventors: STEVEN M. WICK, HELEN J. SCHULTZ, GREGORY R. NELSON, AMIT K. MITRA, STEPHEN M. BERGE

Title: TOPICAL FORMULATIONS AND TRANSDERMAL DELIVERY SYSTEMS CONTAINING 1-ISOBUTYL-1H-IMIDAZO[4,5-C]QUINOLIN-4-AMINE

Assignment: 1

Reel/Frame: 011627/0603 **Recorded:** 06/05/2001 **Pages:** 2

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignor: RIKER LABORATORIES **Exec Dt:** 05/03/2001

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Assignment: 2

Reel/Frame: 011712/0020 **Recorded:** 06/05/2001 **Pages:** 2

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignor: RIKER LABORATORIES **Exec Dt:** 05/03/2001

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US005238944A

United States Patent [19]

Wick et al.

[11] Patent Number: 5,238,944

[45] Date of Patent: Aug. 24, 1993

[54] TOPICAL FORMULATIONS AND TRANSDERMAL DELIVERY SYSTEMS CONTAINING 1-ISOBUTYL-1H-IMIDAZO[4,5-C]QUINOLIN-4-AMINE

[75] Inventors: Steven M. Wick, Mahtomedi; Helen J. Schultz, Falcon Heights, both of Minn.; Gregory R. Nelson, Hudson, Wis.; Amit K. Mitra, Woodbury; Stephen M. Berge, Shoreview, both of Minn.

[73] Assignee: Riker Laboratories, Inc., St. Paul, Minn.

[21] Appl. No.: 845,323

[22] Filed: Mar. 3, 1992

Related U.S. Application Data

[63] Continuation of Ser. No. 444,555, Nov. 30, 1989, abandoned, which is a continuation-in-part of Ser. No. 284,933, Dec. 15, 1988, abandoned.

[51] Int. Cl.[5] A61K 31/44; A61K 31/20

[52] U.S. Cl. 514/293; 514/558; 514/947

[58] Field of Search 514/293, 784, 946, 947, 514/558

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Primary Examiner—Frederick E. Waddell
Assistant Examiner—Raymond J. Henley, III
Attorney, Agent, or Firm—Gary L. Griswold; Walter N. Kirn; Douglas E. Reedich

[57] ABSTRACT

Pharmaceutical formulations and adhesive-coated sheet materials for the topical and/or transdermal delivery of 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine, including creams, ointments and pressure-sensitive adhesive compositions. Pharmacological methods of using the formulations and the adhesive-coated sheet materials of the invention in the treatment of viral infections.

13 Claims, 1 Drawing Sheet

TOPICAL FORMULATIONS AND TRANSDERMAL DELIVERY SYSTEMS CONTAINING 1-ISOBUTYL-1H-IMIDAZO[4,5-C]QUINOLIN-4-AMINE

This is a continuation of application Ser. No. 07/444,555 filed Nov. 30, 1989, now abandoned, which is a continuation-in-part of U.S. Ser. No. 07/284,933 filed Dec. 15, 1988 now abandoned.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention pertains to pharmaceutical formulations for the topical or transdermal delivery of drugs. More particularly, it pertains to creams, ointments, pressure sensitive adhesive coatings, and adhesive-coated sheet materials that contain compounds that enhance skin penetration of drugs.

2. Description of the Related Art

The compound 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine is disclosed in U.S. Pat. No. 4,689,338 and described therein as an antiviral agent and as an interferon inducer. A variety of formulations for topical administration of this compound are also described.

U.S. Pat. No. 4,751,087 discloses the use of a combination of ethyl oleate and glyceryl monolaurate as a skin penetration enhancer for nitroglycerine, with all three components being contained in the adhesive layer of a transdermal patch.

U.S. Pat. No. 4,411,893 discloses the use of N,N-dimethyldodecylamine-N-oxide as a skin penetration enhancer in aqueous systems.

U.S. Pat. No. 4,722,941 discloses readily absorbable pharmaceutical compositions that comprise a pharmacologically active agent distributed in a vehicle comprising an absorption-enhancing amount of at least one fatty acid containing 6 to 12 carbon atoms and optionally a fatty acid monoglyceride. Such compositions are said to be particularly useful for increasing the absorption of pharmacologically active bases.

U.S. Pat. No. 4,746,515 discloses a method of using glyceryl monolaurate to enhance the transdermal flux of a transdermally deliverable drug through intact skin.

SUMMARY OF THE INVENTION

The present invention provides a substantially non-irritating pharmaceutical formulation for topical and/or transdermal administration of the agent 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, which formulation comprises:

a) 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine in an amount of about 0.5 percent to about 9 percent by weight based on the total weight of the formulation; and

b) a pharmaceutically acceptable vehicle for the 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, which vehicle comprises a fatty acid selected from the group consisting of isostearic acid, oleic acid and a combination thereof in a total amount of about 3 percent to about 45 percent by weight based on the total weight of the formulation. The formulation is further characterized in that when tested in the hairless mouse skin model described herein, the formulation provides a penetration of the agent of at least about 10% (and preferably at least about 15%) of the total amount of the agent contained in the formulation in 24 hours.

The salient elements of a pharmaceutical formulation according to the invention are (a) 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine and (b) a fatty acid, i.e., isostearic and/or oleic acid. A pharmaceutical formulation of the invention can be in any form known to the art, such as a cream, an ointment, or a pressure-sensitive adhesive composition, each form containing the necessary elements in particular amounts and further containing various additional elements.

A cream of the invention preferably contains about 1 percent to about 5 percent by weight of 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, based on the total weight of the cream; about 5 percent to about 25 percent by weight of fatty acid, based on the total weight of the cream; and optional ingredients such as emollients, emulsifiers, thickeners, and/or preservatives.

An ointment of the invention contains an ointment base in addition to 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine and fatty acid. An ointment of the invention preferably contains about 0.5 percent to about 9 percent, and more preferably about 0.5 percent to about 5 percent by weight 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine; about 3 percent to about 45 percent, more preferably about 3 percent to about 25 percent by weight fatty acid; and about 60 percent to about 95 percent by weight ointment base, all weights being based on the total weight of the ointment. Optionally, an ointment of the invention can also contain emulsifiers, emollients and thickeners.

A pressure-sensitive adhesive composition of the invention contains 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine, fatty acid, and an adhesive. The adhesives utilized in a pressure sensitive adhesive composition of the invention are preferably substantially chemically inert to 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine. A pressure sensitive adhesive composition of the invention preferably contains about 0.5 percent to about 9 percent by weight, more preferably of about 3 percent to about 7 percent by weight 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine; about 10 percent to about 40 percent by weight, more preferably of about 15 percent to about 30 percent by weight, and most preferably about 20 percent to about 30 percent by weight of fatty acid; all weights being based on the total weight of the pressure sensitive adhesive composition.

Optionally, pressure sensitive adhesive compositions of the invention can also contain one or more skin penetration enhancers. The total amount of skin penetration enhancer(s) present in a pressure sensitive adhesive composition of the invention is preferably about 3 percent to about 25 percent by weight, and more preferably about 3 percent to about 10 percent by weight based on the total weight of the pressure sensitive adhesive composition.

A pressure sensitive adhesive coated sheet material of the invention can be made from a pressure-sensitive adhesive composition of the invention in the form of an article such as a tape, a patch, a sheet, or a dressing.

A formulation of the invention can be used to topically and/or transdermally administer 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine for treating viral infections, for example Type I or Type II Herpes simplex infections.

BRIEF DESCRIPTION OF THE DRAWING

The invention will be described below with reference to the accompanying Drawing, which is an isometric view of a diffusion cell for measuring penetrability of

completely dissolved, the remaining oil phase ingredients are added and heating is continued until dissolution appears to be complete.

The water phase can be prepared by combining all other ingredients and heating with stirring until dissolution appears to be complete.

The creams of the invention are generally prepared by adding the water phase to the oil phase with both phases at a temperature of about 65° C. to 75° C. The resulting emulsion is mixed with a suitable mixer apparatus to give the desired cream.

An ointment of the invention contains an ointment base in addition to 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine and fatty acid.

The amount of 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine present in an ointment of the invention is preferably about 0.5 percent to about 9 percent, and more preferably about 0.5 percent to about 5 percent by weight based on the total weight of the ointment.

The total amount of fatty acid present in an ointment of the invention is preferably about 3 percent to about 45 percent, and more preferably about 3 percent to about 25 percent based on the total weight of the ointment.

A pharmaceutically acceptable ointment base such as petrolatum or polyethylene glycol 400 (available from Union Carbide) in combination with polyethylene glycol 3350 (available from Union Carbide) can be used. The amount of ointment base present in an ointment of the invention is preferably about 60 percent to about 95 percent by weight based on the total weight of ointment.

Optionally, an ointment of the invention can also contain emollients, emulsifiers and thickeners. The emollients, emulsifiers, and thickeners and the preferred amounts thereof described above in connection with creams are also generally suitable for use in an ointment of the invention.

An ointment according to the invention can be prepared by combining 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine with fatty acid and heating with occasional stirring to a temperature of about 65° C. When the 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine appears to be completely dissolved, the remaining ingredients are added and heated to about 65° C. The resulting mixture is mixed with a suitable mixer while being allowed to cool to room temperature.

A pressure-sensitive adhesive composition of the invention contains 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine, fatty acid, and a pressure sensitive adhesive polymer.

The amount of 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine present in a pressure sensitive adhesive composition of the invention is preferably about 0.5 percent to about 9 percent by weight, and more preferably about 3 percent to about 7 percent by weight based on the total weight of the adhesive composition. The amount of fatty acid present is preferably about 10 percent to about 40 percent by weight, more preferably about 15 percent to about 30 percent by weight, and most preferably about 20 percent to about 30 percent by weight, based on the total weight of the adhesive composition.

Preferably, the adhesive polymer utilized in a pressure sensitive adhesive composition of the invention is substantially chemically inert to 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine. The adhesive polymer is preferably present in an amount of about 55 percent to about 85 percent by weight based on the total weight of the composition. Suitable adhesive polymers include acrylic adhesives that contain, as a major constituent (i.e., at least about 80 percent by weight of all monomers in the polymer), a hydrophobic monomeric acrylic or methacrylic acid ester of an alkyl alcohol, the alkyl alcohol containing 4 to 10 carbon atoms. Examples of suitable monomers are those discussed below in connection with the "A Monomer". These adhesive polymers can further contain minor amounts of other monomers such as the "B Monomers" listed below.

Preferred adhesives include acrylic pressure-sensitive adhesive copolymers containing A and B Monomers as follows: Monomer A is a hydrophobic monomeric acrylic or methacrylic acid ester of an alkyl alcohol, the alkyl alcohol containing 4 to 10 carbon atoms, preferably 6 to 10 carbon atoms, more preferably 6 to 8 carbon atoms, and most preferably 8 carbon atoms. Examples of suitable A Monomers are n-butyl, n-pentyl, n-hexyl, isoheptyl, n-nonyl, n-decyl, isohexyl, 2-ethyloctyl, isooctyl and 2-ethylhexyl acrylates. The most preferred A Monomer is isooctyl acrylate.

Monomer B is a reinforcing monomer selected from the group consisting of acrylic acid; methacrylic acid; alkyl acrylates and methacrylates containing 1 to 3 carbon atoms in the alkyl group; acrylamide; methacrylamide; lower alkyl-substituted acrylamides (i.e., the alkyl group containing 1 to 4 carbon atoms) such as tertiary-butyl acrylamide; diacetone acrylamide; n-vinyl-2-pyrrolidone; vinyl ethers such as vinyl tertiary-butyl ether; substituted ethylenes such as derivatives of maleic anhydride, dimethyl itaconate and monoethyl formate and vinyl perfluoro-n-butyrate. The preferred B Monomers are acrylic acid, methacrylic acid, the above-described alkyl acrylates and methacrylates, acrylamide, methacrylamide, and the above-described lower alkyl substituted acrylamides. The most preferred B Monomer is acrylamide.

In one embodiment of a pressure-sensitive adhesive composition of the invention, the pressure-sensitive adhesive copolymer containing A and B Monomers as set forth above preferably contains the A Monomer in an amount by weight of about 80 percent to about 98 percent of the total weight of all monomers in the copolymer. The A Monomer is more preferably present in an amount by weight of about 88 percent to about 98 percent, and is most preferably present in an amount by weight of about 91 percent to about 98 percent. The B Monomer in such a copolymer is preferably present in the pressure-sensitive adhesive copolymer in an amount by weight of about 2 percent to about 20 percent, more preferably about 2 percent to about 12 percent, and most preferably 2 to 9 percent of the total weight of the monomers in the copolymer.

In another embodiment of a pressure-sensitive adhesive composition of the invention, the adhesive copolymer comprises about 60 to about 80 percent by weight (and preferably about 70 to about 80 percent by weight) of the above-mentioned hydrophobic monomeric acrylic or methacrylic acid ester of an alkyl alcohol (i.e., Monomer A described above) based on the total weight of all monomers in the copolymer; about 4 to about 9 percent by weight based on the total weight of all monomers in the copolymer of a reinforcing monomer selected from the group consisting of acrylic acid, methacrylic acid, an alkyl acrylate or methacrylate containing 1 to 3 carbon atoms in the alkyl group, acrylamide, methacrylamide, a lower alkyl-substituted acryl-

lower portions of the cell 21 and 22, which are held together by means of a ball joint clamp 23.

The portion of the cell below the mounted skin was completely filled with 0.1 N hydrochloric acid such that the receptor fluid contacted the skin. The receptor fluid was stirred using a magnetic stir bar 24 and a magnetic stirrer (not illustrated). The sampling port 25 was covered with a material such as Parafilm ® except when in use.

When a cream or ointment was evaluated, approximately 100 mg of the formulation was applied to the epidermal (upper) side of the skin to cover in an even layer only the area of the skin that would be in contact with the receptor fluid when the skin is mounted in the diffusion cell. When an adhesive coated sheet material was evaluated, the skin was mounted on the diffusion cell and a 2.056 cm^2 patch was applied to the skin and pressed to cause uniform contact to the skin. Generally, the cream or the patch was applied to the skin prior to the time the receptor fluid was added to the cell below the skin.

The cell was then placed in a constant temperature (32°±2° C.) chamber. To maintain constant temperature, the chamber utilized a heat exchanger coupled to a constant temperature bath, with a fan to circulate air. The receptor fluid was stirred by means of a magnetic stirring bar throughout the experiment to assure a uniform sample and a reduced diffusion barrier layer on the dermal side of the skin. A sample of receptor fluid was removed at specified times. The withdrawn receptor fluid was analyzed for drug content by conventional high pressure liquid chromatography as follows:

A 15 centimeter column containing Zorbax TM C_8 (an octylsilane, available from E. I. DuPont de Nemours & Company), 5 micron particle size, was used. The mobile phase was 35 percent acetonitrile/65 percent water (volume/volume) containing 0.2 percent tetramethylammonium hydroxide and 0.2 percent 1-dodecanesulfonate sodium, with the pH of the mobile phase adjusted to 2.0 with phosphoric acid. The flow rate was 2 ml per minute. Ultraviolet detection at 254 nanometers was used. The amount of drug penetrating the skin over the specified time period was calculated as a percentage of the dose applied to the skin.

This in vitro method is referred to as the hairless mouse skin model in the claims. For purposes of the claims where this model is referred to the values stated for skin penetration are the average of 4 independent determinations using a different mouse skin for each determination.

In Vivo Test Method

Formulations of the invention can also be evaluated in vivo for their ability to inhibit lesion formation in guinea pigs infected with Herpes simplex virus Type II and for their ability to induce interferon production in guinea pigs.

In the specific test method used herein, care was taken to be sure the formulation had optimal penetration by washing the backs of the guinea pigs with mild detergent before the formulations were applied. One treatment was given at 24 hours preinfection. When a cream or ointment was evaluated, 200 microliters of the formulation was applied topically to the back of the guinea pig, rubbed in, covered with a Hill-top Chamber and then wrapped with Medipore TM brand tape (commercially available from 3M). When an adhesive coated sheet material was evaluated, an article in the form of a patch of a specified size was applied to the back of the guinea pig and wrapped with Medipore TM brand tape. After the patch had been in place for 24 hours, it was removed and the guinea pig was infected with the virus as described below.

Female Hartley guinea pigs (150–200 grams) were abraded in the vaginal area with a dry cotton swab. The guinea pigs were then infected intravaginally with a cotton swab saturated with HSV-2 (1×10^{-5} plaque forming units/ml). The formulations of the invention were evaluated by comparing lesion development in treated and untreated animals. External lesions were scored daily for ten days, unless otherwise specified, using the following scale: 0, no lesion; 1, redness and swelling; 2, a few small vesicles; 3, several large vesicles; 4, large ulcers and necrosis; 5, paralysis. The percent Lesion Inhibition was calculated as follows $100-[(\text{Sum of maximum lesion scores of treated group divided by the Sum of the maximum scores of infected control})\times100]$.

Interferon levels in the guinea pigs was monitored by bleeding via cardiac puncture of anesthetized guinea pigs 17 to 24 hours after dosing. The serum of each animal was separately assayed for interferon activity as follows:

The serum was diluted and incubated with guinea pig fibroblast cells at 37° C. overnight in 96 well microtiter plates. The incubated cells were then challenged with an inoculum of mengovirus that is sufficient to kill untreated cells in two days. Two days after such a challenge, the cells were examined both microscopically and after staining with crystal violet to determine whether the cells remain intact The results were reported as activity/ml. Activity/ml indicates the highest dilution of serum that protects cells from virus challenge. An untreated guinea pig control typically exhibits an activity/ml of less than about 100, although activity/ml has been observed to exceed 100.

Inherent Viscosity Measurement

The inherent viscosity values reported in the Examples below were obtained by the conventional method used by those skilled in the art. The measurement of the viscosity of dilute solutions of the adhesive, when compared to controls run under the same conditions, clearly demonstrates the relative molecular weights. It is the comparative values that are significant; absolute figures are not required. In the examples, the inherent viscosity values were obtained using a Cannon-Fenske #50 viscometer to measure the flow time of 10 ml of a polymer solution (0.2 g polymer/deciliter tetrahydrofuran, in a water bath controlled at 25° C.). The examples and the controls were run under identical conditions. The test procedure followed and the apparatus used are explained in detail in the *Textbook of Polymer Science*, F. W. Billmeyer, Wiley-Interscience, 2nd Edition, 1971 under: Polymer chains and their characterization, D. Solution Viscosity and Molecular Size, pp 84–85, the disclosure of which is incorporated by reference.

The following examples are provided to illustrate the invention, but are not intended to be limiting thereof. Parts and percentages are by weight unless otherwise specified.

TABLE 1

	% by Weight Example 2	3	4	5
Oil Phase				
1-Isobutyl-1H-imidazo-[4,5-c]quinolin-4-amine	1.0	1.0	1.0	1.0
Isostearic acid	10.0	10.0	5.0	5.0
Benzyl alcohol	—	2.0	—	—
Cetyl alcohol	—	1.7	—	—
Stearyl alcohol	—	2.3	—	—
Cetearyl alcohol	6.0	—	6.0	6.0
Polysorbate 60	2.55	2.55	2.55	2.55
Sorbitan monostearate	0.45	0.45	0.45	0.45
Brij TM 30[a]	—	—	—	10.0
Aqueous Phase				
Glycerin	2.0	2.0	2.0	2.0
Methylparaben	0.2	0.2	0.2	0.2
Propylparaben	0.02	0.02	0.02	0.02
Purified water	77.78	77.78	82.78	72.78

Brij TM 30 (polyoxyethylene(4) lauryl ether) is available from ICI Americas, Inc.

TABLE 2

	% by Weight Example 6	7	8	9
Oil Phase				
1-Isobutyl-1H-imidazo-[4,5-c]quinolin-4-amine	1.0	1.0	1.0	1.0
Isostearic acid	10.0	25.0	10.0	6.0
Benzyl alcohol	—	2.0	—	2.0
Cetyl alcohol	—	2.2	1.7	—
Stearyl alcohol	—	3.1	2.3	—
Cetearyl alcohol	6.0	—	—	6.0
Polysorbate 60	2.55	3.4	2.55	2.55
Sorbitan monostearate	0.45	0.6	0.45	0.45
Brij TM 30	10.0	—	—	—
Aqueous Phase				
Glycerin	2.0	2.0	2.0	2.0
Methylparaben	0.2	0.2	0.2	0.2
Propylparaben	0.02	0.02	0.02	0.02
Purified water	67.78	60.48	79.78	79.78

EXAMPLE 10

A cream according to the present invention was prepared from the following ingredients:

	% by Weight	Amount
Oil Phase		
1-Isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine	1.0	3.00 g
Isostearic acid	5.0	15.0 g
White petrolatum	15.0	45.0 g
Light mineral oil	12.8	38.4 g
Aluminum stearate	8.0	24.0 g
Cetyl alcohol	4.0	12.0 g
Witconol TM 14[a]	3.0	9.00 g
Acetylated lanolin	1.0	3.0 g
Propylparaben	0.063	0.19 g
Aqueous Phase		
Veegum TM K[b]	1.0	3.0 g
Methylparaben	0.12	0.36 g
Purified water	49.017	147.05 g

[a]Witconol TM 14 (polyglyceryl-4 oleate) is available from Witco Chemical Corp. Organics Division
[b]Veegum TM K (colloidal magnesium aluminum silicate) is available from R. T. Vanderbilt Company Inc.

The materials listed above were combined according to the following procedure:

The 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine and theisostearic acid were weighed into a glass jar and heated with occasional stirring until the amine was dissolved (the temperature reached 68° C.). To this solution was added, the petrolatum, mineral oil, aluminum stearate, cetyl alcohol, Witconol TM 14, acetylated lanoline and propylparaben. The mixture was heated to 75° C. In a separate beaker, the methylparaben and water were combined and heated until the paraben dissolved (the temperature reached 61° C.). The Veegum TM K was added to the aqueous solution and heated at 75° C. for 30 minutes while mixing with a homogenizer. With both phases at 75° C., the aqueous phase was slowly added to the oil phase while mixing with a homogenizer. Mixing was continued for 30 minutes while maintaining a temperature to about 80° C. The jar was then capped and the formulation was allowed to cool.

EXAMPLE 11

An ointment according to the present invention was prepared from the following ingredients:

	% by Weight	Amount
1-Isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine	1.0	0.20 g
Isostearic acid	5.0	1.00 g
Mineral oil	12.8	2.56 g
White petrolatum	65.2	13.04 g
Cetyl alcohol	4.0	0.80 g
Acetylated lanolin	1.0	0.20 g
Witconol TM 14	3.0	0.60 g
Aluminum stearate	8.0	1.60 g

The materials listed above were combined according to following procedure:

The 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine and the isostearic acid were placed in a glass jar and heated with stirring until the amine was dissolved. The remaining ingredients were added and the resulting mixture was heated to 65° C. and then mixed while being allowed to cool to room temperature.

EXAMPLE 12

Using the general procedure of Example 11 an ointment containing the following ingredients was prepared.

	% by Weight	Amount
1-Isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine	1.0	0.20 g
Isostearic acid	6.0	1.20 g
Polyethylene Glycol 400	55.8	11.16 g
Polyethylene Glycol 3350	32.6	6.52 g
Stearyl alcohol	4.6	0.92 g

EXAMPLES 13–15

Creams of the present invention were prepared using the ingredients shown in Table 3. The Example 1 except that benzyl alcohol was used with the isostearic acid to dissolve the 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine.

TABLE 3

	Example 13	14	15
	% by Weight		
Oil Phase			

age penetration in 24 hours was 46.5% of the applied dose.

EXAMPLE 19 and COMPARATIVE EXAMPLE 20

Using the method described in Example 18, the formulations shown below were prepared and the penetration through hairless mouse skin measured. The adhesive used was a copolymer of isooctyl acrylate:acrylic acid (94:6) and had an inherent viscosity of 1.45–1.60 dl/g in ethyl acetate. The solvent used was heptane:isopropanol (70:30). Patches that measured 2.056 cm^2 were employed. Three independent determinations were carried out and the results were averaged.

Formulation	Average Percent Penetration in 24 hours
Example 19	
3.0% 1-Isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine (micronized) 15% Isostearic acid 82% adhesive	20.5 ± 6.4
Comparative Example 20	
3.1% 1-Isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine (micronized) 96.9% adhesive	4.0 ± 1.5

This example shows that a pressure-sensitive adhesive coated sheet material of the invention exhibits superior penetration of 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine as compared to one not containing a fatty acid.

EXAMPLES 21–45

Using the method described in Example 18, the formulations shown in Table 7 below were prepared and the penetration through hairless mouse skin was measured. The adhesive used was the copolymer of isooctyl acrylate:acrylamide (93:7), prepared in PREPARATIVE METHOD 1 above. The solvent was 90:10 ethyl acetate:methanol. The 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine used was micronized. All formulations were mixed at room temperature unless otherwise indicated. Patches that measured 2.056 cm^2 were used and four independent determinations were carried out for each formulation unless otherwise indicated and the results were averaged.

TABLE 7

EXAMPLE	ADHESIVE	AMINE	% By Weight ISO	OLEIC	EO	GML	OTHER	HMS
21	82.1	2.9	15.0					22.5[e] ± 1.76
22[a]	78.8	3.0	15.0			3.2		32.4 ± 1.44
23[a]	72.0	3.0	15.0		10.0			33.8 ± 2.62
24[a]	75.5	3.0	15.0		5.0	1.5		33.3 ± 2.17
25[a]	71.9	3.0		51.9	10.0			39.9 ± 5.73
26[a]	76.9	3.0		20.1				42.2 ± 1.68
27	68.3	3.0	6.0	9.1	12.1	1.5		33.8 ± 5.38
28	69.7	3.0	6.0	9.1	12.1			26.5 ± 2.61
29	70.0	3.0	6.0	13.0	8.0			44.3 ± 7.69
30	66.9	3.0		20.0	10.0			33.2 ± 7.78
31	72.0	3.0	15.0				10.0[c]	28.4 ± 3.48
32	71.9	3.0		15.0			10.1[d]	33.3 ± 2.90
33	65.2	3.0	6.0	13.1	8.1	1.5	3.1[b]	46.3 ± 3.44
34	65.4	3.0	9.0	18.0		1.6	3.0[b]	74.5 ± 3.10
35	64.0	3.0	10.0	20.0		1.6	1.5[b]	81.4 ± 5.36
36	63.9	3.0	30.0			1.5	1.6[b]	75.3 ± 5.21
37	63.8	3.0		30.1		1.5	1.5[b]	80.6 ± 5.41
38	60.1	3.1	10.0	19.8	5.5	1.5		89.3 ± 4.97
39	58.7	3.0	10.1	19.8	5.8	1.6	1.0[b]	88.0 ± 0.29
40	61.9	3.0	10.0	20.0	5.0			69.0 ± 3.00
41	60.2	3.0	10.3	20.0	5.0		1.5[b]	80.0 ± 1.24
42	58.8	3.5	10.1	20.0	5.1	1.5	1.0[b]	86.0 ± 0.78
43	58.3	4.0	10.2	20.2	5.0	1.5	1.0[b]	84.0 ± 2.01
44	57.5	4.5	9.9	20.0	5.4	1.5	1.1[b]	84.0 ± 3.61
45	57.3	5.1	10.1	20.0	5.0	1.5	1.0[b]	87.0 ± 7.23

AMINE = 1-Isobutyl-1H-imidazo[4,5-c]quinolin-4-amine
ISO = Isostearic acid
OLEIC = Oleic acid
EO = Ethyl oleate
GML = Glyceryl monolaurate (available from Lauricidin, Inc., Monroe, Michigan, under the trade designation Lauricidin.
HMS = % Penetration in 24 hours in hairless mouse skin model
[a]Horizontal shaker placed in 40° C. constant temperature room
[b]N,N-Dimethyldodecylamine-N-oxide
[c]Isopropyl myristrate
[d]Diisopropyl adipate
[e]Used 3 independent determinations

EXAMPLES 46–48

Pressure-Sensitive Adhesive Coated Sheet Materials Prepared Using Unmicronized 1-Isobutyl-1H-imidazo[4,5-c]quinolin-4-amine

Using the general method of Example 18 the formulations shown below were prepared. 1-Isobutyl-1H-imidazo[4,5-c]quinolin-4-amine that had been ground with a mortar and pestle was used. The adhesive was the 93:7 isooctyl acrylate:acrylamide copolymer prepared in PREPARATIVE METHOD 1 above. The solvent was 90:10 ethyl acetate:methanol. All formulations were mixed at room temperature.

	Example 46	47	48
1-Isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine	3.0	3.0	3.0
Ethyl oleate	5.1	5.0	8.0
Isostearic acid	10.0	10.0	6.0
Oleic acid	20.0	20.0	13.0
Glyceryl monolaurate	1.5	1.5	1.5
N,N-dimethyldodecylamine-N-oxide	1.0	1.1	3.0

weight based on the total weight of said formulation.

6. A formulation according to claim 3 wherein said 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine is present in an amount of about 1 percent to about 5 percent by weight based on the total weight of said formulation.

7. A formulation according to claim 4, comprising about 1 percent of said 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, about 10 percent of said isostearic acid, about 2 percent benzyl alcohol, about 2.2 percent cetyl alcohol, about 3.1 percent stearyl alcohol, about 2.55 percent polysorbate 60, about 0.45 percent sorbitan monostearate, about 2 percent glycerin, about 0.2 percent methylparaben, about 0.02 percent propylparaben and about 76.48 percent purified water, all percentages being based on the total weight of said formulation.

8. A formulation according to claim 4, comprising about 1 percent of said 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, about 10 percent of said isostearic acid, about 6 percent cetearyl alcohol, about 2.55 percent polysorbate 60, about 0.45 percent sorbitan monostearate, about 2 percent glycerin, about 0.2 percent methylparaben, about 0.02 percent propylparaben and about 77.78 percent purified water, all percentages being based on the total weight of said formulation.

9. A formulation according to claim 4, comprising about 1 percent of said 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, about 10 percent of said isostearic acid about 2 percent benzyl alcohol, about 1.7 percent cetyl alcohol, about 2.3 percent stearyl alcohol, about 2.55 percent polysorbate 60, about 0.45 percent sorbitan monostearate, about 2 percent glycerin, about 0.2 percent methylparaben, about 0.02 percent propylparaben and about 77.78 percent purified water, all percentages being based on the total weight of said formulation.

10. A formulation according to claim 4, comprising about 5 percent of said 1-isobutyl-1H-imidazo-[4,5-c]quinolin-4-amine, about 25 percent of said isostearic acid, about 2 percent benzyl alcohol, about 2.2 percent cetyl alcohol, about 3.1 percent stearyl alcohol, about 3 percent petrolatum, about 3.4 percent polysorbate 60, about 0.6 percent sorbitan monostearate, about 2 percent glycerin, about 0.2 percent methylparaben, about 0.02 percent propylparaben and about 53.48 percent purified water, all percentages being based on the total weight of said formulation.

11. A formulation according to claim 4, comprising about 1 percent of said 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, about 5 percent of said isostearic acid, about 15 percent petrolatum, about 12.8 percent light mineral oil, about 8 percent aluminum stearate, about 4 percent cetyl alcohol, about 3 percent polyglyceryl-4 oleate, about 1 percent acetylated lanolin, about 0.063 percent propylparaben, about 1 percent Veegum K, about 0.12 percent methylparaben and about 49.02 percent purified water, all percentages being based on the total weight of said formulation.

12. A method of topical and/or transdermal administration of 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine for treating a viral disease in a mammal, which method comprises

(1) placing a formulation according to claim 1 on the skin of a mammal; and

(2) allowing said formulation to remain in contact with the skin for a sufficient time to permit an effective amount of the 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine to penetrate the skin to achieve the antiviral effect.

13. A method of topical and/or transdermal administration of 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine to induce interferon biosynthesis in a mammal, which method comprises

(1) placing a formulation according to claim 1 on the skin of a mammal; and

(2) allowing said formulation to remain in contact with the skin for a sufficient time to permit an effective amount of 1-isobutyl 1H-imidazo[4,5-c]-quinolin-4-amine to penetrate the skin to induce interferon biosynthesis.

* * * * *

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Part 3

Patent Assignment Abstract of Title

NOTE:Results display only for issued patents and published applications. For pending or abandoned applications please consult USPTO staff.

Total Assignments: 4

Patent #: 4689338 **Issue Dt:** 08/25/1987 **Application #:** 06798385 **Filing Dt:** 11/15/1985

Inventor: JOHN F. GERSTER

Title: 1H-IMIDAZO(4,5-C)QUINOLIN-4-AMINES AND ANTIVIRAL USE

Assignment: 1

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Assignment: 3

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Assignors: 3M INNOVATIVE PROPERTIES COMPANY **Exec Dt:** 07/01/2003

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United States Patent [19]
Gerster

[11] Patent Number: 4,689,338
[45] Date of Patent: Aug. 25, 1987

[54] 1H-IMIDAZO[4,5-C]QUINOLIN-4-AMINES AND ANTIVIRAL USE

[75] Inventor: John F. Gerster, Woodbury, Minn.

[73] Assignee: Riker Laboratories, Inc., St. Paul, Minn.

[21] Appl. No.: 798,385

[22] Filed: Nov. 15, 1985

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 553,158, Nov. 18, 1983, abandoned.

[51] Int. Cl.[4] C07D 471/04; A61K 31/47
[52] U.S. Cl. 514/293; 546/82; 546/159
[58] Field of Search 546/82; 514/293

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[57] ABSTRACT

1H-Imidazo[4,5-c]quinolin-4-amines which are antivirals. Pharmacological methods of using such compounds and pharmaceutical compositions containing such compounds are also described.

22 Claims, No Drawings

radical such as in the case of the substituents alkoxy and alkyl (other than R_1 and R_2 as alkyl) preferably contain one or two carbon atoms in each alkyl radical.

The preferred cyclic alkyl substituents contain six or seven carbon atoms.

The halogen substituents which may be contained in the compounds of the instant invention are selected from fluorine, chlorine and bromine. Preferred halogen substituents are fluorine and chlorine.

When R is alkoxy it is preferably methoxy.

It is preferred that n of Formula I be zero or one. It is most preferred that n of Formula I be zero.

If R_1 is substituted benzyl, (phenyl)ethyl or phenyl, it is preferred that the benzene ring be monosubstituted. It is most preferred that the benzyl, (phenyl)ethyl or phenyl substituent be unsubstituted. As used in the instant specification and claims, "(phenyl)ethyl" denotes 1-(phenyl)ethyl or 2-(phenyl)ethyl.

It is presently preferred that R_1 be alkyl, benzyl, cyclohexylmethyl or hydroxyalkyl.

When R_1 is hydroxyalkyl, the compounds of the invention may contain one to three hydroxy substituents. Preferred hydroxyalkyl groups contain one or two hydroxy substituents.

Presently preferred compounds are:

1-methyl-1H-imidazo[4,5-c]quinolin-4-amine;

1,2,8-trimethyl-1H-imidazo[4,5-c]quinolin-4-amine;

1-(2-hydroxyethyl)-1H-imidazo[4,5-c]quinolin-4-amine;

1-benzyl-1H-imidazo[4,5-c]quinolin-4-amine;

1,2-dimethyl-1H-imidazo[4,5-c]quinolin-4-amine;

1-benzyl-2-methyl-1H-imidazo[4,5-c]quinolin-4-amine;

1,8-dimethyl-1H-imidazo[4,5-c]quinolin-4-amine;

1-cyclohexylmethyl-1H-imidazo[4,5-c]quinolin-4-amine;

1-(2,3-dihydroxypropyl)-1H-imidazo[4,5-c]quinolin-4-amine;

1-n-hexyl-2-methyl-1H-imidazo[4,5-c]quinolin-4-amine;

1-n-butyl-1H-imidazo[4,5-c]quinolin-4-amine;

1,2-diisobutyl-1H-imidazo[4,5-c]quinolin-4-amine;

1-n-hexyl-1H-imidazo[4,5-c]quinolin-4-amine;

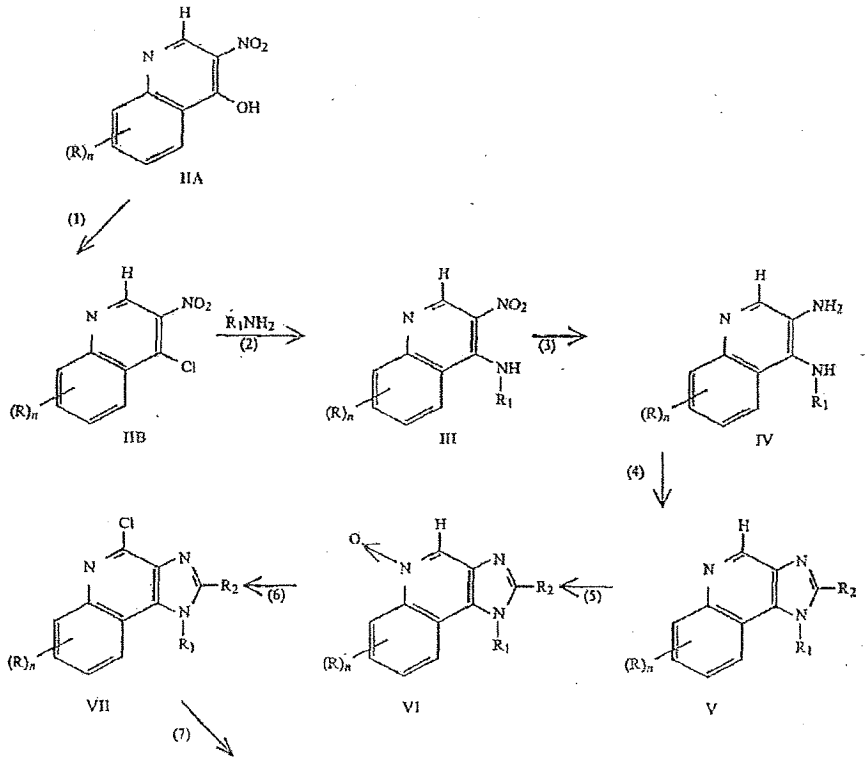
1-(2-hydroxy-2-methylpropyl)-1H-imidazo-[4,5-c]quinolin-4-amine; and

1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine.

The presently most preferred compound is the last one mentioned above.

The compounds of the invention of Formula I are prepared as described in the Reaction Scheme illustrated below, wherein R, R1, R2 and n are as defined above:

Reaction Scheme



of average molecular weight of about 400, commercially available from Union Carbide Corporation), or in a polyethyleneglycol cream. The drugs are applied topically (e.g., intravaginally or cutaneously), for example, twice daily for a predetermined number of days, for example, five days. Application is initiated at a predetermined interval either before or after infection such as one hour after infection. Virus replication can be monitored by determining the amount of virus recovered with vaginal swabs taken, for example, on days 1, 2, 3, 5 or 7 after infection. Virus is eluted from the swab in 1 ml of cell growth medium (Medium 199, Gibco Laboratories, Grand Island, New York) and virus titer is determined using cell monolayers. External lesions are scored daily for 10 days using the following scale: zero, no lesion; 1, redness or swelling; 2, a few small vesicles; 3, several large vesicles; 4, large ulcers and necrosis; 5, paralysis. Percent inhibition of lesion development is determined by comparing untreated, but infected control animals and drug treated animals. Comparison studies with known drugs such as phosphonacetic acid and acyclovir may also be conducted. The compounds of the invention inhibit lesion development in that they reduce the number of lesions and the severity thereof. It has been found that the compound 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine is efficacious when administered to guinea pigs beginning as earlier as 7 days before infection or as late as 72 hours after infection.

The compound 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine of the invention not only exhibits activity against primary lesions, but exhibits activity against recurrent lesions as well. Such activity may be demonstrated using the method described by Stanberry, et al., Journal of Infectious Diseases, 146, 397–404 (1982). Guinea pigs treated with a suspension of 1.0% of the compound in a 5% "Tween 80" water solution were found to experience fewer episodes of recurrent lesions and recurrent lesions lasted for fewer days than in the case of controls. In the foregoing study, the compound was administered topically to the lesions every 12 hours for 21 days beginning 41 days after intravaginal inoculation with Herpes simplex virus Type II. It is believed that other compounds of the invention would exhibit activity against recurrent lesions as well.

In the preferred antiviral method of the invention the compounds of Formula I are used to control Type I or Type II Herpes simplex virus by applying to a population thereof an amount of a compound of Formula I sufficient to attain said control.

The method of the invention is preferably used in vivo for treating infections caused by the viruses, especially in mammals. The method is generally effective when a compound of Formula I or a formulation thereof is administered topically (e.g., intravaginally or on the skin), for example, to a genital herpes infection. The compounds of Formula I may also be used to treat a genital herpes infection by oral administration. Compounds of Formula I are also generally active against herpes infections by intraperitoneal administration. The preferred route of administration is topical.

It has also been found that several compounds of the invention including 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine and 4-amino-1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-c]quinoline (a metabolite of 1-isobutyl-1H-imidazo-[4,5-c]quinolin-4-amine in the guinea pig) induce the biosynthesis of interferon in the guinea pig following a single intravaginal or oral dose of the antiviral compound, and hence the compound is an immunomodulator. The assay employed was that described in Green et al., J. Clin. Microbiology, 12 (3), 433–438 (1980) and Overall et al, J. Interferon Research 4, 529–533 (1984), both incorporated herein by reference, except that guinea pig fibroblasts were used as the cell system and EMC or mengovirus was used as the infecting virus (see Example 198) in evaluating the compounds of the invention. As shown in Example 199, induction of interferon was also observed in the monkey in response to 1-isobutyl-1H-imidazo[4,5-c]quinoline.

While not wishing to be bound to any mechanism, it is believed that the antiviral activity exhibited by the compounds of the invention is attributable to immunomodulation including interferon induction, and it is believed that all compounds of the invention would induce interferon. Further, the fact that interferon is induced suggests that the compounds of the invention could be useful in treating other disease states such as rheumatoid arthritis, warts, eczema, and cancer.

Compounds of the invention are formulated for the various routes of administration in known, pharmaceutically accepted vehicles such as water or polyethylene glycol. Suitable formulations for topical application will generally contain less than 10% by weight of a compound of Formula I, and will preferably contain about 0.1% to 5% by weight of a compound of Formula I.

The compounds of the invention are preferably administered in water which contains either a surfactant such as the "Tween 80" discussed above or cellulose. A 5% concentration of the surfactant has been found to be generally useful in topical, oral and intraperitoneal formualations. The presently preferred antiviral formulation for topical administration is a cream containing 1% by weight of the preferred antiviral compound 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine in micronized form (i.e., particle size of 1–2 microns in diameter); 0.2% by weight of methyl paraben; 0.02% by weight of propyl paraben; 5% by weight of "Avicel CL-611" (a colloidal form of microcrystalline cellulose which has been coprocessed with sodium carboxymethyl cellulose (available from FMC Corporation, Philadelphia, Pennsylvania); and 93.78% by weight of water. The formulation is prepared by dry-mixing the antiviral compound with the "Avicel CL-611", and then combining that mixture with a solution containing the methyl paraben and propyl paraben in the water.

The following examples are provided to illustrate the invention and are not intended to be limiting thereof.

EXAMPLE 1

Preparation of a Compound of Formula III

To a stirred solution of 50.0g (0.24 mole) of 4-chloro-3-nitroquinoline in 300 ml of tetrahydrofuran was added, in small portions, 52.7g (0.72 mole) of isobutylamine. The mixture was heated at its reflux temperature for one hour, and was then evaporated in vacuo. Water was added to the residue and the solid was separated by filtration. The solid was suspended in one liter of water, and was dissolved by the gradual addition of concentrated hydrochloric acid (to pH 3 to 4), at which time the solution was filtered. The filtrate was basified (to pH 9 to 10) by the addition of concentrated ammonium hydroxide to provide bright yellow 4-(isobutylamino)-3-nitroquinoline, m.p. 119°–121° C. The structural assignment was supported by infrared spectral analysis.

TABLE III-continued

Ex. No.	Intermediate of Formula IV (Example No.)	Ortho Ester; Carboxylic Acid	Intermediate of Formula V (m.p. in °C.)
34	19	triethyl orthoformate; formic acid	1-(2-hydroxyethyl)-1H—imidazo[4,5-c]quinoline (170–172)
35	20	triethyl orthoacetate; acetic acid	1-(2,3-dihydroxypropyl)-2-methyl-1H—imidazo[4,5-c]-quinoline (232–234)
36	21	triethyl orthoacetate; acetic acid	1-ethyl-2-methyl-1H—imidazo[4,5-c]quinoline (126–129)
37	22	triethyl orthoformate; formic acid	1,8-dimethyl-1H—imidazo-[4,5-c]quinoline hydrate (180–184)
38	22	triethyl orthoacetate; acetic acid	1,2,8-trimethyl-1H—imidazo-[4,5-c]quinoline (220–221)
39	21	triethyl orthoformate; formic acid	1-ethyl-1H—imidazo[4,5-c]-quinoline (80–82)
40	23	triethyl orthoformate; formic acid	1-isobutyl-8-methyl-1H—imidazo[4,5-c]quinoline (160–163)
41	24	triethyl orthoformate; formic acid	8-fluoro-1-methyl-1H—imidazo[4,5-c]quinoline hydrate (201–205)
42	25	triethyl orthoformate; formic acid	7-chloro-1-isobutyl-1H—imidazo[4,5-c]quinoline (not taken)
43	26	triethyl orthoformate; formic acid	1-phenyl-1H—imidazo-[4,5-c]quinoline (137–139)
44	27	triethyl orthoformate; formic acid	1-(4-methoxyphenyl)-1H—imidazo[4,5-c]quinoline (150–152)
45	28	triethyl orthoacetate; acetic acid	1-(4-fluorophenyl)-2-methyl-1H—imidazo-[4,5-c]quinoline (191–193)
46	27	triethyl orthoacetate; acetic acid	1-(4-methoxyphenyl)-2-methyl-1H—imidazo[4,5-c]-quinoline (174–176)
47	28	triethyl orthoformate; formic acid	1-(4-fluorophenyl)-1H—imidazo[4,5-c]quinoline (159–161)
48	29	triethyl orthoformate; formic acid	1-(n-butyl)-1H—imidazo-[4,5-c]quinoline (not taken)
49	30	triethyl orthoformate; formic acid	1-(3-hydroxypropyl)-1H—imidazo[4,5-c]quinoline (not taken)
50	17	triethyl orthoformate; formic acid	1-methyl-1H—imidazo-[4,5-c]quinoline (143–145)
51	20	triethyl orthoformate; formic acid	1-(2,3-dihydroxypropyl)-1H—imidazo[4,5-c]quinoline (228–230)
52	16	triethyl orthoacetate; acetic acid	1-isobutyl-2-methyl-1H—imidazo[4,5-c]quinoline hydrate (85–88)
53	24	triethyl orthoacetate; acetic acid	1,2-dimethyl-8-fluoro-1H—imidazo[4,5-c]quinoline (234–239)

EXAMPLE 54

Preparation of a Compound of Formula VI.

To a solution of 9.3g (0.0413 mole) of 1-isobutyl-1H-imidazo [4,5-c]quinoline (from Example 32) in 150 ml of acetic acid was added 1.5 equivalents (0.062 mole) of 30% hydrogen peroxide. The mixture was heat at 65°–70° C. for one day, and was then evaporated. The residue was neutralized with saturated sodium bicarbonate solution, and the resulting mixture was extracted with dichloromethane. The extracts were dried, and were then evaporated to provide a residue which solidifed gradually to yellow solid 1-isobutyl-1H-imdazo [4,5-c]quinolin-5-oxide. This product was recrystallized twice from ethyl acetate to give a green solid, m.p. 211°–213° C. Analysis: calculated for $C_{14}H_{15}N_3O$: %C, 69.7; %7; %H, 6.3; %N, 17.4; Found %C, 69,7; %H, 6.3; %N, 17.1.

Using the method of Example 54 intermediate compounds of Formula VI show in Table IV were prepared.

TABLE IV

Ex. No.	Intermediate of Example V (Example No.)	Intermediate of Formula VI (m.p. in. °C.)
55	31	1,2-dimethyl-1H—imidazo[4,5-c]quinolin-5-oxide (234–237)
56	33	8-chloro-1,2-dimethyl-1H—imidazo[4,5-c]-quinolin-5-oxide (not taken)
57	124 (Part C)	1-benzyl-1H—imidazo[4,5-c]-quinolin-5-oxide (241–251)
58	126 (Part C)	1-cyclohexylmethyl-1H—imidazo[4,5-c]-quinolin-5-oxide (224–226, dec.)
59	36	1-ethyl-2-methyl-1H—imidazo[4,5-c]-quinolin-5-oxide (220–222)
60	37	1,8-dimethyl-1H—imidazo[4,5-c]quinolin-5-oxide (265–268)
61	38	1,2,8-trimethyl-1H—imidazo[4,5-c]quinolin-5-oxide (not taken)
62	39	1-ethyl-1H—imidazo[4,5-c]quinolin-5-oxide (not taken)
63	40	1-isobutyl-8-methyl-1H—imidazo[4,5-c]-quinolin-5-oxide (not taken)
64	41	8-fluoro-1-methyl-1H—imidazo[4,5-c]-quinolin-5-oxide (not taken)
65	42	7-chloro-1-isobutyl-1H—imidazo[4,5-c]-quinolin-5-oxide (not taken)
66	43	1-phenyl-1H—imidazo[4,5-c]quinolin-5-oxide (222–225)
67	44	1-(4-methoxyphenyl)-1H—imidazo[4,5-c]-quinolin-5-oxide (245–247)
68	45	1-(4-fluorophenyl)-2-methyl-1H—imidazo-[4,5-c]quinolin-5-oxide (245–248)
69	46	1-(4-methoxyphenyl)-2-methyl-1H—imidazo-[4,5-c]quinolin-5-oxide (211–213)
70	47	1-(4-fluorophenyl)-1H—imidazo[4,5-c]-quinolin-5-oxide (257–259)
71	136	2-methyl-1-[2-(phenyl)ethyl]-1H—imidazo-[4,5-c]quinolin-5-oxide (204–206)
72	130 (Part B)	1-[2-(phenyl)ethyl]-1H—imidazo[4,5-c]-quinolin-5-oxide (73–95)
73	50	1-methyl-1H—imidazo[4,5-c]quinolin-5-oxide (241–244)
74	131	1-benzyl-2-methyl-1H—imidazo[4,5-c]quinolin-5-oxide (193–196)
75	52	1-isobutyl-2-methyl-1H—imidazo[4,5-c]-quinolin-5-oxide (214–216)
76	53	1,2-dimethyl-8-fluoro-1H—imidazo[4,5-c]-quinolin-5-oxide (not taken)

EXAMPLE 77

Preparation of a Compound of Formula VII

A mixture of 9.95 g (0.0412 mole) of 1-isobutyl-1H-imidazo [4,5-c]quinolin-5-oxide (from Example 54) and 100 ml of phosphorus oxychloride was heated at its reflux temperature for 2.5 hours, and was then cooled and poured into ice with stirring. Basification (to pH 9–10) with 50% aqueous sodium hydroxide solution was followed by extraction with dichloromethane. The extracts were dried over sodium chloride and sodium bicarbonate, and were then evaporated to provide a solid residue. A sample of the residue was recrystallized from diethyl ether to provide 4-chloro-1-isobutyl-1H-imidazo [4,5-c]quinoline, m.p. 134°–136° C. Analysis: Calculated for $C_{14}H_{17}ClN_3$: %C, 64.7; H, 5.4; %N, 16.2; Found: %C, 64.3; %H, 5.3; %N, 16.3.

methanol to provide tan solid 1-(2-benzoyloxyethyl)-1H-imidazo[4,5-c]-quinolin-5-oxide.

EXAMPLE 117

A mixture of 50g (0.15 mole) of 1-(2-benzoyloxyethyl)-1H-imidazo[4,5-c]quinolin-5-oxide (from Example 116) and 200 ml of phosphorus oxychloride was heated for two hours on a steam bath. The mixture was then partially evaporated in vacuo. The mixture was poured over ice, and the solution was neutralized with sodium hydroxide. The product was separated by filtration and dissolved in dichloromethane, and the solution was washed with aqueous sodium bicarbonate solution and dried. Evaporation provided a solid which was recrystallized from a 50:50 methanol:dichloromethane solution to provide white 1-(2-benzoyloxyethyl)-4-chloro-1H-imidazo[4,5-c]quinoline, m.p. 186°–190,C. Analysis: Calculated for $C_{19}H_{14}ClN_3O_2$; % C, 64.9; % H, 4.0; % N, 12.0; Found: % C, 64.8; % H, 3.8; % N, 12.1.

EXAMPLE 118

A mixture of 25.3 g (0.072 mole) of 1-(2-benzoyloxyethyl)-4-chloro-1H-imidazo[4,5-c]quinoline (from Example 117) and 500 ml of 10% ammonia in methanol was stirred at about 20° C. for three days, and was then filtered and finally evaporated to low volume. The slurry was mixed with diethyl ether, and the solid was separated by filtration, washed with ether and recrystallized from methanol to provide white crystals of 4-chloro-1-(2-hydroxyethyl)-1H-imidazo[4,5-c]quinoline, m.p. 185°–187° C. Analysis: Calculated for $C_{12}H_{10}ClN_3O$: % C, 58.2; % H, 4.1; N, 17.0; Found: % C, 58.0; % H, 4.0; % N, 17.3.

EXAMPLE 119

A mixture of 1.3 g (0.0037 mole) of 1-(2-benzoyloxyethyl)-4-chloro-1H-imidazo[4,5-c]quinoline (from Example 117) in 60 ml of methanol was saturated with about 10g of ammonia gas. The mixture was heated at 150° C. in a steel bomb for ten hours. The mixture was evaporated, and the residue was slurried in diethyl ether and filtered. The solid obtained was slurried in methanolic hydrochloric acid to provide off-white solid 1-(2-hydroxyethyl)-1H-imidazo[4,5-c]quinolin-4-amine hydrochloride hydrate, m.p. >250° C. Analysis: Calculated for $C_{12}H_{12}N_4O{\cdot}HCl{\cdot}1.25H_2O$: C, 50.2; % H, 5.4; % N, 19.5; Found: % C, 50.2; % H, 5.2; % N, 19.1.

EXAMPLE 120

Part A

Using the method of Example 115, benzoyl chloride was reacted with 1-(2,3-dihydroxypropyl)-1H-imidazo[4,5-c]-quinoline (from Example 51) to provide 1-(2,3-dibenzoyloxypropyl)-1H-imidazo[4,5-c]quinoline.

Part B

The crude product from Part A was reacted with hydrogen peroxide according to the method of Example 116 to provide 1-(2,3-dibenzoyloxypropyl)-1H-imidazo[4,5-c]-quinolin-5-oxide as a pale yellow solid, the melting point of the crude material being 73°–82° C.

Part C

The product from Part B was reacted with phosphorus oxychloride according to the method of Example 117 to provide 4-chloro-1-(2,3-dibenzoyloxypropyl)-1H-imidazo[4,5-c]quinoline, m.p. 162°–165° C. after recrystallization from ethanol. Analysis: Calculated for $C_{27}H_{20}ClN_3O_4$: % C, 66.7; % H, 4.1; % N, 8.6; Found: % C, 66.3; H, 3.9; % N, 8.4.

Part D

Hydrolysis of the product from Part C according to the method of Example 118 to provide 4-chloro-1-(2,3-dihydroxypropyl)-1H-imidazo[4,5-c]quinoline.

EXAMPLE 121

Part A

1-(2,3-Dihydroxypropyl)-1H-imidazo[4,5-c]quinoline (from Example 51) was reacted with excess acetic anhydride to provide 1-(2,3-diacetoxypropyl-1H-imidazo[4,5-c]quinoline.

Part B

The product of Part A was reacted with hydrogen peroxide according to the method of Example 116 to provide 1-(2,3-diacetoxypropyl)-1-H-imidazo[4,5-c]quinolin-5-oxide as a brownish-yellow solid, the crude melting point of which being 84°–96° C. Recrystallization from ethanol provided solid product, m.p. 223°–225° C. Analysis: Calculated for C13H12ClN302 % C, 56.2, % H, 4.4; N, 15.1; Found: % C, 55.8, % H, 4.3; % N, 15.1.

EXAMPLE 122

To a stirred solution of 4.0 g (0.0117 mole) of 1-(2,3-diacetoxypropyl)-1H-imidazo[4,5-c]quinolin-5-oxide (from Example 121, Part A) in 50 ml of methanol was added about 12 drops of 25% sodium methoxide solution. After one hour the product was collected by filtration, washed with methanol and recrystallized from ethanol to provide 1-(2,3-dihydroxypropyl)-1H-imidazo[4,5-c]quinolin-5-oxide, m.p. 240°–242° C. Analysis: Calculated for $C_{13}H_{13}N_3O_3$: % C, 60.2; % H, 5.1; % N, 16.2; Found: % C, 60.0; % H, 5.0; % N, 15.8.

EXAMPLE 123

Excess acetic anhydride (100 ml) was refluxed for 0.5 hour with 1-(2,3-dihydroxypropyl)-2-methyl-1H-imidazo[4,5-c]quinoline (from Example 35) to provide 1-(2,3-diacetoxypropyl)-2-methyl-1H-imidazo[4,5-c]quinoline. This product was reacted with hydrogen peroxide using the method of Example 120 to provide 1-(2,3-diacetoxypropyl)- 2-methyl-1H-imidazo[4,5-c]quinolin-5-oxide as a yellow solid. This crude product was reacted with phosphorus oxychloride according to the method of Example 121 to provide the product 4-chloro-(2,3-diacetoxypropyl)-2-methyl-1H-imidazo[4,5-c]quinoline. This product was dissolved in methanol saturated with ammonia and stirred for three days. The product obtained was 4-chloro-1-(2,3-dihydroxypropyl)-2-methyl-1H-imidazo[4,5-c]quinoline.

EXAMPLE 124

Part A

Using the method of Example 1, benzylamine and 4-chloro-3-nitroquinoline were reacted to provide 4-benzylamino-3-nitroquinoline. The structural assignment for the crude product (m.p. 178°–196° C.) was supported by infrared spectral analysis.

with water and dried to provide yellow solid 4-methylamino-3-nitroquinoline, m.p. 167°–171° C.

EXAMPLE 135

To a solution of 4.8 g (0.0311 mole) of phosphorus oxychloride in 20 ml of N,N-dimethylformamide was added in small portions 5.0 g (0.0207 mole) of 1-isobutyl-1H-imidazo[4,5-c]quinolin-5-oxide. The solution was stirred for 15 minutes at 20° C., then heated on a steam bath for 15 minutes. The solution was cooled to 20° C., then poured into stirred ice. The solution was basified to pH 8 with concentrated ammonium hydroxide. The yellow solid precipitate was separated by filtration, washed sequentially with water and diethyl ether, and dried to provide 4-chloro-1-isobutyl-1H-imidazo[4,5-c]quinoline hydrate, m.p. 103°–107° C. Recrystallization twice from ethyl acetate with drying provided 4-chloro-1-isobutyl-1H-imidazo[4,5-c]-quinoline, m.p. 135°–137° C. Analysis: Calculated for $C_{14}H_{14}ClN_3$: % C, 64.7; % H, 5.4; % N, 16.2; Found: % C, 64.6; H, 5.5; % N, 16.1.

EXAMPLE 136

Using the method of Example 31, 3-amino-4-[2-(phenyl)ethylamino]quinoline (from Example 130, Part A) was reacted with triethyl orthoacetate and acetic acid to provide 2-methyl-1-[2-(phenyl)ethyl]-1H-imidazo[4,5-c]-quinoline.

EXAMPLE 137

Alternative Preparation of a Compound of Formula I

A mixture of 6.0 g (0.023 mole) of 4-chloro-1-isobutyl-1H-imidazo[4,5-c]quinoline (from Example 77) and 30 ml of 20% ammonia in methanol was heated in a steel bomb for 18 hours at 150° C. The bomb was cooled, and the solid was separated by filtration, washed with methanol and recrystallized from N,N-dimethylformamide to provide 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, m.p. 292°–294° C. Analysis: Calculated for $C_{14}H_{16}N_4$: % C, 70.0; H, 6.7; % N, 23.3; Found: % C, 69.9; % H, 6.7; % N, 23.6.

EXAMPLE 138

Step (1)

To a solution of 22.5 g (0.0823 mole) of 4-(n-hexyl-)amino-3-nitroquinoline in 300 ml of toluene was added about 1.0 g of 5% platinum on charcoal and the mixture was hydrogenated on a Paar apparatus for 1.5 hours. Filtration followed by evaporation in vacuo provided a residue of 3-amino-4-(n-hexyl)aminoquinoline as an orange solid. Thin layer chromatographic analysis of the product on silica gel, eluting with methanol, showed one spot at R_f=0.73 and a trace at Rf=0.35.

Step (2)

The crude reaction product obtained by the method of Step (1) above from 22.5 g of 4-(n-hexyl)amino-3-nitroquinoline was mixed with 17.1 (0.1152 mole) of triethyl orthoformate and the mixture was heated at 130° C. for 2.5 hours. Evaporation provided a residue which was analyzed by thin layer chromatography on a silica gel plate, eluting with methanol. One spot was detected at R_f=0.8. A small sample of the residue was recrystallized once from diethyl ether to provide solid 1-(n-hexyl)-1H-imidazo-4,5-c]quinoline, m.p. 75°–77° C. Analysis: Calculated for $C_{16}H_{19}N_3$: % C, 75.85; % H, 7.55; % N, 16.6; Found:% C, 75.7; % H, 7.7; % N, 16.7

Step (3)

The crude reaction product from Step (2) above was diluted with 125 ml of glacial acetic acid and 14.0 g (0.1235 mole) of 30% hydrogen peroxide, and the mixture was heated at a bath temperature of 70° C. for 22 hours. The glacial acetic acid was removed by adding heptane and by then effecting an azeotropic distillation. The residue was diluted and neutralized with saturated sodium bicarbonate solution. The solid obtained was separated by filtration, washed with water, slurried in diethyl ether, separated by filtration and dried. Recrystallization from ethyl acetate provided 11.8 g of solid 1-(n-hexyl)-1H-imidazo[4,5-c]-quinolin-5-oxide, m.p. 153°–158° C.

Step (4)

To a mixture of 6.1 ml (0.0657 mole) of phosphorus oxychloride and 80 ml of N,N-dimethylformamide was added gradually, with cooling to 10°–20° C., 11.8 g (0.0438 mole) of 1-(n-hexyl)-1H-imidazo[1,5-c]quinolin-5-oxide. The solution was allowed to stand at 20° C. for 15 minutes, and was then heated on a steam bath for 30 minutes. The solution was cooled and poured over ice with stirring. To the mixture was added concentrated ammonium hydroxide to adjust the pH to 8 to 9. The solid was separated by filtration, washed sequentially with water and diethyl ether, and dried. Recrystallization of a small portion of product from 1:1 ethyl acetate;hexane provided white solid 4-chloro-1-(n-hexyl)-1H-imidazo[4,5-c]quinoline, m.p. 106°–108° C. Analysis: Calculated for $C_{16}H_{18}ClN_3$; % C 66.8; H, 6.3; % N, 14.6; Found % C, 66.8; % H, 6.1: % N, 14.4.

Step (5)

A mixture of 8.9 g (0.0308 mole) of 4-chloro-1-(n-hexyl)-1H-imidazo[4,5-c]quinoline and 75 ml of 20% ammonia in methanol was placed in a metal bomb and heated at 150° C. for about 8 hours. After cooling, the solid was separated by filtration, washed with methanol and recrystallized from ethanol. The product was white solid 1-(n-hexyl)-1H-imidazo[4,5-c]quinolin-4-amine, m.p. 189°–191° C. Analysis: Calculated for $C_{16}H_{20}N_4$ % C, 71.6; H, 7.5; % N, 20.9; Found: % C, 71.4; % H, 7.4; % N, 21.0.

Using the method of Example 1 and/or 2, and starting with the indicated substituted quinolines and primary amines, the following compounds of Formula III were prepared (Table II).

TABLE VII

Ex. No.	Quinoline Starting Material of Formula IIB	Primary Amine Starting Material	Intermediate of Formula III (m.p. in. °C.)
139	4-chloro-3-nitroquinoline	4-chlorobenzylamine	4-(4-chlorobenzylamino)-3-nitroquinoline (175–177)
140	4-chloro-3-nitroquinoline	n-octylamine	4-(n-octylamino)-3-nitroquinoline (50–52)
141	4-chloro-3-nitroquinoline	1-(phenyl)ethylamine	4-[1-(phenyl)ethylaminol]-3-nitroquinoline (138–141)
142	4-chloro-3-nitroquinoline	1,3-dimethylbutylamine	4-(1,3-dimethylbutylamino)-3-nitroquinoline (66–68)

Using the general method exemplified in Example 138, Step (5), compounds of the invention of Formula I shown in Table XI were prepared.

TABLE XI

Ex. No.	Intermediate of Formula VII (Example No.)	Product of Formula I (m.p. in °C.)
175	82	1-ethyl-2-methyl-1H—imidazo[4,5-c]quinolin-4-amine (274–276)
176	164	2-methyl-1-[2-(phenyl)ethyl]-1H—imidazo[4,5-c]quinolin-4-amine (188–190)
177	165	1-(4-chlorobenzyl)-2-methyl-1H—imidazo[4,5-c]quinolin-4-amine (>300)
178	166	1-(n-butyl)-1H—imidazo[4,5-c]quinolin-4-amine (274–276)
179	94	1-[2-(phenyl)ethyl]-1H—imidazo[4,5-c]quinolin-4-amine (199–201)
180	167	1-(n-hexyl)-2-methyl-1H—imidazo[4,5-c]quinolin-4-amine (189–191)
181	168	2-isobutyl-1-methyl-1H—imidazo[4,5-c]quinolin-4-amine (222–224)
182	169	1-(n-octyl)-1H—imidazo[4,5-c]quinolin-4-amine (127–129)
183	170	1,2-diisobutyl-1H—imidazo[4,5-c]quinolin-4-amine (191–193)
184	171	2-isobutyl-1-[2-(phenyl)ethyl]-1H—imidazo[4,5-c]quinolin-4-amine hydrate (232–235)
185	172	1-[1-(phenyl)ethyl]-1H—imidazo[4,5-c]quinolin-4-amine (217–221)
186	173	1-(1,3-dimethylbutyl)-1H—imidazo[4,5-c]quinolin-4-amine (158–161)

EXAMPLE 187

To a solution of 3.5 g (0.0116 mole) of 2-methyl-1-[2-(phenyl)ethyl]-1H-imidazo[4,5-c]quinolin-4-amine in 30 ml of ethanol was added 1.2 g (0.0127 mole) of methanesulfonic acid. The mixture was heated on a steam bath for 30 minutes, the ethanol was removed by evaporation in vacuo and the residue was recrystallized from ethanol. The product was white solid 2-methyl-1-[2-(phenyl)ethyl]-H-imidazo[4,5-c]quinolin-4-amine methanesulfonate, m.p. 287°–289° C. Analysis: Calculated for $C_{19}H_{18}N_4.CH_3S_3O_3H$: % C, 0.3; % H, 5.6; % N, 14.1; Found: % C, 60.1; % H, 5.3; % N, 14.0.

Additional salts of the invention prepared by reaction of the amine with acids in ethanol as described above were:

1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine hydrochloride, m.p. >300° C.

1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine nitrate salt, m.p. 260°–262° C. (dec.)

1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine methanesulfonate hydrate, m.p. 203°–205° C.

1-n-hexyl-1H-imidazo[4,5-c]quinolin-4-amine hydrochloride, m.p. 288°–291° C.

1,2-diisobutyl-1H-imidazo[4,5-c]quinoline-4-amine hydrochloride hydrate.

EXAMPLE 188

Step (A)

To 50.0 g (0.269 mole) of 4-hydroxy-3-nitroquinoline in 300 ml of N,N-dimethylformamide in a 500 ml erlenmeyer flask was added, gradually, 44.3 g (0.2892 mole) of phosphorus oxychloride. The resulting mixture was heated on a steam bath for about 15 minutes, and was then poured onto ice with stirring. After neutralization with saturated sodium bicarbonate solution, the resulting light-colored solid was separated by filtration and washed sequentially with a saturated sodium bicarbonate solution and water. The solid was dissolved in methylene chloride and the solution obtained was dried over sodium chloride, filtered and transferred to a 2 l erlenmeyer flask. Triethylamine (159.6 g, 1.577 moles) was added at one time, followed by the slow addition of 21.2 g (0.2892 mole) of isobutylamine. After the isobutylamine had been added, the mixture was heated on a steam bath for about 30 minutes. The methylene chloride was removed by rotary evaporation. Water was added to the residue obtained, and concentrated hydrochloric acid was subsequently added to dissolve the residue. The solution was filtered, and the filtrate was brought to pH 8–9 with concentrated ammonium hydroxide. The resulting yellow solid was filtered, washed with water, and dried to provide 73.4 g of crude 4-isobutylamino-3-nitroquinoline, m.p. 114°–118° C. The product was further purified by recrystallization from ethanol.

Step (B)

4-Isobutylamino-3-nitroquinoline (31.5 g, 0.1284 moles) from Step (A) above, was dissolved in 300 ml of toluene, and about one g of platinum on charcoal was added thereto. The resulting mixture was hydrogenated on a Parr apparatus for one and one-half hours. The mixture was then heated and filtered. Toluene was removed from the filtrate by rotary evaporation to provide 27.8 g of crude 3-amino-4-(isobutylamino)quinoline. Recrystallization twice from ethyl acetate/hexane provided 18.8 g of purified product, m.p. 98°–100° C. Analysis: Calculated for $C_{13}H_{17}N_3$: % C, 72.5; % H, 8.0; % N, 19.5; Found: % C, 73.2; % H, 7.8; % N, 19.7.

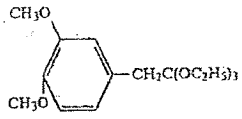
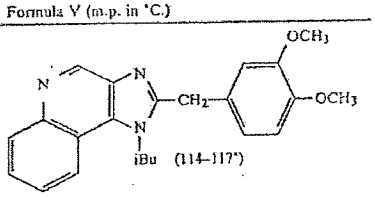
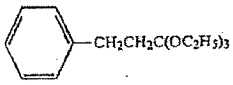
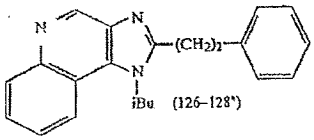
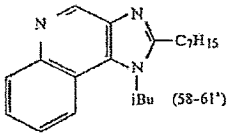
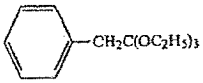
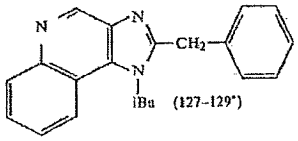
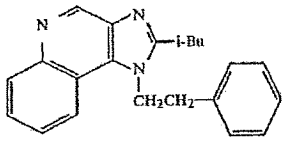
Step (C)

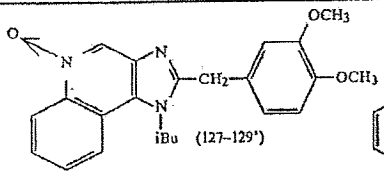
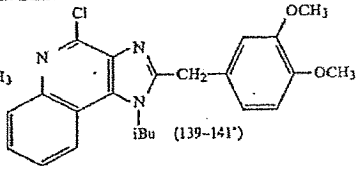
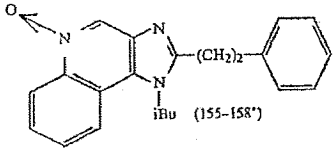
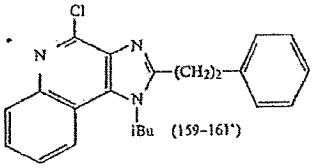
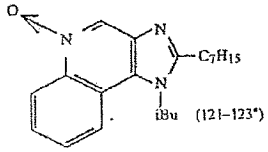
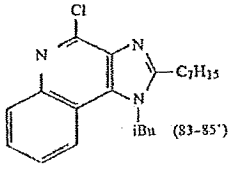
To 10.0 g (0.0464 mole) of 3-amino-4-(isobutylamino)quinoline (from Step (B) above) was added 9.0 g (0.0604 mole) of triethyl orthoformate, and the mixture was heated at 125°–130° C. for three hours. The mixture was then allowed to cool to room temperature, and 30 ml of glacial acetic acid and 7.9 g (0.0696 mole) of 30% hydrogen peroxide solution were added thereto. The resulting mixture was heated at 68°–70° C. in an oil bath for about 24 hours. The glacial acetic acid was removed by azetropic distillation using heptane as the entrainer. Saturated sodium bicarbonate solution was added to the residue to bring it to neutrality. The beige solid which precipitated was filtered, washed with water, and dried to provide 10.0 g of crude product 1-isobutyl-1H-imidazo[4,5-c]quinolin-5-oxide. This solid was slurried in a small amount of cold acetone, and was then separated by filtration, washed and dried to provide 6.2 g of purified product having a m.p. of 205°–209° C.

Step (D)

To 40 ml of cold N,N-dimethylformamide (10°–20° C.) was added slowly 5.9 g (0.0385 mole) of phosphorus oxychloride with swirling, the temperature of the mixture being maintained at 10–20° C. 1-Isobutyl-1H-imidazo[4,5-c]quinolin-5-oxide (6.2 g; 0.0257 mole) from Step (C) above was added gradually with swirling and

TABLE XII-continued

Example	Formula IV	Trialkyl ortho ester	Formula V (m.p. in °C.)
190	Example 16		 iBu (114–117°)
191	Example 16		 iBu (126–128°)
192	Example 16	$CH_3(CH_2)_6C(OC_2H_5)_3$	 iBu (58–61°)
193	Example 16		 iBu (127–129°)
194	Example 129	i-Bu—$C(OC_2H_5)_3$	 (92–94°)

Example	Compound of Formula VI (m.p. °C.)	Compound of Formula VII (m.p. in °C.)
190	 iBu (127–129°)	 iBu (139–141°)
191	 iBu (155–158°)	 iBu (159–161°)
192	 iBu (121–123°)	 iBu (83–85°)

EXAMPLE 195

Step A

To a solution of 24.5 g (0.1 mole) of 4-(isobutylamino)-3-nitroquinoline in 500 ml of toluene was added about 1 g of platinum on charcoal, and the mixture was hydrogenated on a Paar apparatus. The catalyst was then removed by filtration.

Step B

To the solution from Step A was added 10.6 g (0.1 mole) of benzaldehyde, and the solution was refluxed under a Dean StCark trap until no more water came over. The product was 28.3 g of a bright yellow oil after evaporation of the solvent. Thin layer chromatography revealed two spots and therefore the oil was chromatographed using a flash column and ethyl acetate as the eluent to provide 14 g of a yellow solid which appeared homogeneous by thin layer chromatography, but smelled of benzaldehyde. The solid was dissolved in toluene and 5 g of palladium on charcoal was added. After refluxing overnight, the catalyst was filtered, the toluene was evaporated and the solid was recrystallized from ethyl acetate to provide colorless crystals of 1-isobutyl-2-phenyl-1H-imidazo[4,5-c]quinoline, melting point 139°–140° C. Analysis: Calculated for $C_{20}H_{19}N$: % C, 79.7; % H, 6.4; % N, 13.9; Found: % C, 79.7, % H, 6.2; % N, 13.9.

Step C

To a solution of 7.0 g (0.0232 mole) of 1-isobutyl-2-phenyl-1H-imidazo[4,5-c]quinoline in 50 ml of acetic acid was added 3.9 g (0.035 mole) of hydrogen peroxide in the form of a 30% aqueous solution. The mixture was heated at 70° C. for one day, and was then evaporated, added to water and made basic with ammonia and filtered. The product was 6.8 g of 1-isobutyl-2-phenyl-1H-imidazo[4,5-c]quinolin-5-oxide.

Step D

Three ml (0.0321 mole) of phosphorus oxychloride and 35 ml of N,N-dimethyl formamide were mixed and 6.8 g (0.0214 mole) of 1-isobutyl-2-phenyl-1H-imidazo[4,5-c]quinolin-5-oxide was added thereto. The solution was heated on a steam batch for 30 minutes, and was then cooled and poured into ice with stirring. Basification (to pH 9–10) with ammonium hydroxide was followed by extraction with dichloromethane. The extracts were dried with magnesium sulfate, and were then evaporated to provide an oil which was slurried in hexane. The material solidified and was washed with hexane and dried to yield 6.8 g of a solid which was mainly 4-chloro-1-isobutyl-2-phenyl-1H-imidazo[4,5-c]quinoline as shown by thin layer chromatography.

Step E

A mixture of 5.6 g (0.016 mole) of 4-chloro-1-isobutyl-2-phenyl-1H-imidazo[4,5-c]quinoline and 30 ml of a 20% mixture of ammonia in methanol was placed in a metal bomb and heated at 145°–150° C. for about 6 hours. After cooling, the solid was separated by filtration, washed with methanol and dried to provide 3.8 g of crude product. Recrystallization of the solid from ethanol provided 2.4 g of colorless 1-isobutyl-2-phenyl-1H-imidazo[4,5-c]quinolin-4-amine hydrate, melting point 194°–205° C. Analysis: Calculated for $C_{20}H_{20}N_4 \cdot \frac{1}{3}H_2O$: % C, 73.8; % H, 6.5; % N, 17.2. Found: % C, 73.6; % H, 6.2; % N, 17.0

EXAMPLE 196

Step A

Following the general method of Example 195, Step A, 4-(methylamino)-3-nitroquinoline was reduced to provide 3-amino-4-(methylamino)quinoline.

Step B

Following the general method of Example 195, Step B, 3-amino-4-(methylamino)quinoline was reacted with benzaldehyde to provide 1-methyl-2-phenyl-1H-imidazo[4,5-c]quinoline, melting point 168–170° C. Analysis: Calculated for $C_{17}H_{13}N_3$: % C, 78.7; % H, 5.1; % N, 16.2. Found: % C, 78.9; % H, 5.0; % N, 16.1.

Step C

Following the general method of Example 195, Step C, 1-methyl-2-phenyl-1H-imidazo[4,5-c]quinoline was converted to 1-methyl-2-phenyl-1H-imidazo[4,5-c]quinolin-5-oxide.

Step D

Following the general method of Example 195, Step D, 1-methyl-2-phenyl-1H-imidazo[4,5-c]quinolin-5-oxide was converted to 4-chloro-1-methyl-2-phenyl-1H-imidazo[4,5-c]quinoline, melting point 205°–208° C. Analysis: Calculated for $C_{17}H_{12}ClN_3$: % C, 69.5; % H, 4.1; % N, 14.3. Found: % C, 69.0; % H, 4.0; % N, 13.9.

Step E

Following the general method of Example 195, Step E, 4-chloro-1-methyl-2-phenyl-1H-imidazo[4,5-c]quinoline was converted to 1-methyl-2-phenyl-1H-imidazo[4,5-c]quinolin-4-amine, melting point 275°–280° C. Analysis: Calculated for $C_{17}H_{14}N_4$: % C, 74.4; % H, 5.1; % N, 20.4. Found: % C, 74.1; % H, 4.8; % N, 20.7.

EXAMPLE 197

Step A

Following the general method of Example 195, Step B, 3-amino-4-(isobutylamino)quinoline was reacted with veratraldehyde to provide 2-(3,4-dimethoxyphenyl)-1-isobutyl-1H-imidazo[4,5-c]quinoline, melting point 192°–199° C. Analysis: Calculated for $C_{20}H_{23}N_3O_2$: % C, 73.1; % H, 6.4; % N, 11.6. Found: % C, 72.7; % H, 6.3; % N, 11.4.

Step B

Following the general method of Example 195, Step C, 2-(3,4-dimethoxyphenyl)-1-isobutyl-1H-imidazo[4,5-c]quinoline was converted to 2-(3,4-dimethoxyphenyl)-1-isobutyl-1H-imidazo[4,5-c]quinolin-5-oxide.

Step C

Following the general method of Example 195, Step D, 2-(3,4-dimethoxyphenyl)-1-isobutyl-1H-Imidazo[4,5-c]quinoline was converted to 4-chloro-2-(3,4-dimethoxyphenyl)-1-isobutyl-1H-imidazo[4,5-c]quinoline.

Step D

Following the general method of Example 195, Step E, 4-chloro-2-(3,4-dimethoxyphenyl)-1-isobutyl-1H-imidazo[4,5-c]quinoline was converted to 2-(3,4-dimethoxyphenyl)-1-isobutyl-1H-imidazo[4,5-c]quinolin-4-

integer from 1 to 2, with the proviso that if n is 2, then said R groups together contain no more than 6 carbon atoms; or a pharmaceutically acceptable acid addition salt thereof.

2. A compound according to claim 1 wherein R_2 is hydrogen.

3. A compound according to claim 2 wherein R is hydrogen.

4. A compound according to claim 1, wherein R_1 is alkyl, benzyl, cyclohexylmethyl or hydroxyalkyl.

5. A compound according to claim 1, wherein R_1 is alkyl of one to about eight carbon atoms.

6. A compound according to claim 1, wherein R_1 is alkyl of about four to about six carbon atoms.

7. The compound 1-methyl-1H-imidazo[4,5-c]quinolin-4-amine according to claim 1.

8. The compound 1,2,8-trimethyl-1H-imidazo[4,5-c]quinolin-4-amine according to claim 1.

9. The compound 1-(2-hydroxyethyl)-1H-imidazo[4,5-c]quinolin-4-amine according to claim 1.

10. The compound 1,2-dimethyl-1H-imidazo[4,5-c]quinolin-4-amine according to claim 1.

11. The compound 1,8-dimethyl-1H-imidazo[4,5-c]quinolin-4-amine according to claim 1.

12. The compound 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine according to claim 1.

13. The compound 1-(2,3-dihydroxypropyl)-1H-imidazo[4,5-c]quinolin-4-amine according to claim 1.

14. The compound 1-cyclohexylmethyl-1H-imidazo[4,5-c]quinolin-4-amine according to claim 1.

15. The compound 1-benzyl-1H-imidazo[4,5-c]quinolin-4-amine according to claim 1.

16. The compound 1-benzyl-2-methyl-1H-imidazo[4,5-c]quinolin-4-amine according to claim 1.

17. The compound 1-n-hexyl-1H-imidazo[4,5-c]quinolin-4-amine according to claim 1.

18. The compound 1-n-hexyl-2-methyl-1H-imidazo[4,5-c]quinolin-4-amine according to claim 1.

19. An antiviral pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier, said compound being present in an amount sufficient to exert antiviral activity.

20. A method for treating a mammal infected with a virus comprising administering a compound according to claim 1 to said mammal in an amount effective to reduce severity of or prevent the infection.

21. A method treating a mammal infected with Type I or Type II Herpes simplex virus comprising administering a compound according to claim 1 to said mammal in an amount sufficient to inhibit development of lesions caused by said virus.

22. A method according to claim 21, wherein said compound is administered topically to a lesion caused by said virus.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,689,338

DATED : August 25, 1987

INVENTOR(S) : John F. Gerster

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Col. 16, line 3, "% C, 66.3; H, 3.9;" should be --%C, 66.3; %H, 3.9;--

Col. 16, line 8, "to provide" should be --provided--

Col. 16, line 24, "84°-96°C. Recrystallization" should be --84°-96°C. (New Paragraph) Part C (New Paragraph) The product of Part B was reacted with phosphorus oxychloride according to the method of Example 117 to provide 4-chloro-1-(2,3-diacetoxypropyl)-1H-imidazo[4,5-c]-quinoline. (New Paragraph) Part D (New Paragraph) The product of Part C was hydrolyzed according to the method of Example 118 to provide 4-chloro-1-(2,3-dihydroxypropyl)-1H-imidazo[4,5-c]quinoline. Recrystallization--

Col. 16, line 26, "C13H12ClN302" should be $C_{13}H_{12}ClN_3O_2$:--

Col. 16, line 27, "4.4; N, 15.1; should be --4.4; %N, 15.1;--

Col. 17, line 18, "78.7; H, 5.1;" should be --78.7; %H, 5.1;--

Col. 17, line 42, "Calculated for $C_{16}H_{19}N_3O_2$% C," should be --Calculated for $C_{16}H_{19}N_3O_2$: %C,--

Col. 17, line 63, "68.2; H, 7.4;" should be --68.2; %H, 7.4;--

Col. 18, line 34, "1-benzyl-4-o" should be --1-benzyl-4---

Col. 18, Line 40, "75.0: %H" should be --75.0; %H--

Col. 19, line 21, "64.6; H, 5.5;" should be --64.6; %H, 5.5;--

Col. 19, line 41, "70.0; H," should be --70.0; %H,--

Col. 19, line 47, "4-(n-hexyl-" should be --4-(n-hexyl)---

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,689,338

DATED : August 25, 1987

INVENTOR(S) : John F. Gerster

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Col. 31, line 14, "Dean StCark" should be --Dean Stark--

Col. 33, line 38, Table XIII, "1-amine" should be --4-amine--

Col. 34, line 2, "sufficiCent" should be --sufficient--

Signed and Sealed this

Twenty-seventh Day of December, 1988

Attest:

Attesting Officer

DONALD J. QUIGG

Commissioner of Patents and Trademarks

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.: 4,689,338

DATED: August 25, 1987

INVENTOR(S): John F. Gerster

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Col. 35, lines 7-8 , claim 3 should read -- A compound according to claim 2, wherein n is the integer 0. --

Signed and Sealed this

Third Day of June, 1997

Attest:

BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks

ALTANA | Product Formulation No.: 0432-100.02 | Page No. 1 of 2

Product: IMIQUIMOD CREAM 5% | Batch No.:

Batch Size: 100 kg | Yield: Theor. 100 kg | Actual: % | Chkd by/Date issued:

R.M.No.	Ingredient	Lot No.	Label Amt. Percent w/w	Formulation Percent w/w	Batch Quantity 100.0 kg	Quantity Dispensed	Weighed By	Checked By	Date Added
	PART A:								
R1309	1. Oleic Acid NF		25.0	25.0	25.0 kg				
R0097	2. Benzyl Alcohol NF		2.000	2.000	2.000 kg				
R1292	3. Imiquimod		5.000	5.000	5.000 kg (1)				
R0438	4. Polysorbate 60 NF		3.40	3.40	3.40 kg				
R0568	5. Sorbitan Monostearate NF		0.60	0.60	0.60 kg				
R1013	6. Cetyl Alcohol NF		2.00	2.00	2.00 kg				
R0414	7. Stearyl Alcohol NF		3.00	3.00	3.00 kg				
R1200	8. White Petrolatum USP		5.00	5.00	5.00 kg				
R0051	9. Propylparaben NF		0.0200	0.0200	0.0200 kg				
	PART B:								
R0980	10. Purified Water USP		50.28	50.28	50.3 kg				
R0026	11. Glycerin USP		3.00	3.00	3.00 kg				
R0019	12. Methylparaben NF		0.2000	0.2000	0.2000 kg				
R1235	13. Xanthan Gum NF		0.50	0.50	0.50 kg				

REMARKS:

See page 2.

Approved By Product Development Date	Approved By Quality Assurance Date	Dispensing Started
Approved By Regulatory Affairs Date	Effective Date / Ist Batch No.	Compounding Completed

ALTANA	Product Formulation No.: 0432-100.02	Page No. 2 of 2
Product: IMIQUIMOD CREAM 5%		Batch No.:

Batch Size: 100 kg	Yield: Theor. 100 kg	Actual:	%	Chkd.by/Date issued:

REMARKS

(1) If the potency of Imiquimod is less than 100%, adjust the quantity to reflect 100% of label potency.

$$\frac{\text{Batch Quantity (kilograms)}}{\text{Assay \% x 0.01}} = \text{Quantity to dispense (kilograms)}$$

Lot No.: _____ use _____ kg @ _____ %
Lot No.: _____ use _____ kg @ _____ %

Calculated By:_____ Date:_____ Checked By:_____ Date:_____

Approved By Product Development	Date	Approved By Quality Assurance	Date	Dispensing Started
Approved By Regulatory Affairs	Date	Effective Date	1st Batch No.	Compounding Completed

Part 4

EXHIBIT D

CLAIM CHART SHOWING INGRINGEMENT OF U.S. PATENT NO. 7,655,672

U.S. Patent No. 7,655,672	**Nycomed generic imiquimod oleic acid cream**
CLAIM 1	
A pharmaceutical cream for topical application to a dermal or mucosal surface for topical delivery of 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine (imiquimod), said pharmaceutical cream comprising:	Nycomed's generic imiquimod is a pharmaceutical cream for topical application to a dermal or mucosal surface for topical delivery of 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine (imiquimod). *See, Appendix 3 of the Nycomed ANDA Letter of January 10, 2007 (Exhibit C); Nordsiek Affidavit at ¶11.*
a therapeutically effective amount of imiquimod; and	Nycomed's generic imiquimod includes 5% imiquimod. This is a therapeutically effective amount of imiquimod. *See Appendix 3 of the Nycomed ANDA Letter (Exhibit C); Nordsiek Affidavit at ¶12.*
a pharmaceutically acceptable vehicle including an oleic acid component,	Nycomed's generic imiquimod uses a pharmaceutically acceptable vehicle including an oleic acid component. *See Appendix 3 of the Nycomed ANDA Letter (Exhibit C); Nordsiek Affidavit at ¶13.*
wherein the oleic acid component at or prior to formulation of said pharmaceutical cream contains at least about 80% oleic acid by weight as a fatty acid, and	In order for the oleic acid component in Nycomed's generic imiquimod-oleic acid cream to be stable, it must comprise at least about 80% oleic acid by weight as a fatty acid.

	Nordsiek Affidavit at ¶13-17, 19.
wherein the oleic acid component at or prior to formulation of said pharmaceutical cream has a peroxide value of less than about 5 milliequivalents of oxygen per kilogram and contains less than about 1% by weight polar impurities, and	In order for the oleic acid component in Nycomed's generic imiquimod-oleic acid cream to be stable, it must have a peroxide value of less than about 5 milliequivalents of oxygen per kilogram, and contain less than about 1% by weight polar impurities. *Nordsiek Affidavit at ¶¶13-17, 19.*
wherein said pharmaceutical cream contains imiquimod-related impurities in an amount of no more than about 0.03% wt./wt. after storage of said pharmaceutical cream at ambient conditions for about 15 days, when absorbance of said pharmaceutical cream is analyzed at about 308 nm using a UV detector.	Because Nycomed's generic imiquimod-oleic acid cream formulation contains the same excipients as reported in Table 2 (columns C and D) of the '672 patent and an oleic acid component refined as described in ¶ 17 of the Nordsiek Affidavit, and because imiquimod is a very stable molecule, Nycomed's generic imiquimod must have imiquimod-related impurities in an amount of no more than about 0.03% wt./wt. after storage of said pharmaceutical cream at ambient conditions for about 15 days, when absorbance of said pharmaceutical cream is analyzed at about 308 nm using a UV detector. *See '672 Patent, Table 2 (Exhibit B); Nordsiek Affidavit ¶¶ 20-24.*
CLAIM 5	
The pharmaceutical formulation of claim 1, wherein the imiquimod is present in an amount of about 5% by weight based on the total	Nycomed's generic imiquimod is a pharmaceutical formulation of claim 1 wherein the imiquimod is present in an amount of about

weight of said pharmaceutical cream	5% by weight based on the total weight of said pharmaceutical cream. *See, Appendix 3 of the Nycomed ANDA Letter of January 10, 2007 (Exhibit C); Nordsiek Affidavit at* ¶25.
and wherein the oleic acid component is present in an amount of no more than about 30% by weight based on the total.	The oleic acid component in Nycomed's generic imiquimod is present in an amount of no more than about 30% by weight based on the total. *See, Appendix 3 of the Nycomed ANDA Letter of January 10, 2007 (Exhibit C); Nordsiek Affidavit at* ¶26.
CLAIM 7	
A pharmaceutical cream for topical application to a dermal or mucosal surface for topical delivery of 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine (imiquimod), said pharmaceutical cream comprising:	Nycomed's generic imiquimod is a pharmaceutical cream for topical application to a dermal or mucosal surface for topical delivery of 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine (imiquimod). *See, Appendix 3 of the Nycomed ANDA Letter of January 10, 2007 (Exhibit C); Nordsiek Affidavit at* ¶11.
a therapeutically effective amount of imiquimod; and	Nycomed's generic imiquimod includes 5% imiquimod. This is a therapeutically effective amount of imiquimod. *See Appendix 3 of the Nycomed ANDA Letter (Exhibit C); Nordsiek Affidavit at* ¶12.
a pharmaceutically acceptable vehicle including an oleic acid component,	Nycomed's generic imiquimod uses a pharmaceutically acceptable vehicle including an oleic acid component. *See Appendix 3 of*

	the Nycomed ANDA Letter (Exhibit C); Nordsiek Affidavit at ¶13.
wherein the oleic acid component at or prior to formulation of said pharmaceutical cream contains at least about 80% oleic acid by weight as a fatty acid, and	In order for the oleic acid component in Nycomed's generic imiquimod-oleic acid cream to be stable, it must comprise at least about 80% oleic acid by weight as a fatty acid. *Nordsiek Affidavit at ¶13-17, 19.*
wherein the oleic acid component at or prior to formulation of said pharmaceutical cream has a peroxide value of less than about 5 milliequivalents of oxygen per kilogram and contains less than about 1% by weight polar impurities, and	In order for the oleic acid component in Nycomed's generic imiquimod-oleic acid cream to be stable, it must have a peroxide value of less than about 5 milliequivalents of oxygen per kilogram, and contain less than about 1% by weight polar impurities. *Nordsiek Affidavit at ¶¶13-17, 19.*
wherein said pharmaceutical cream contains imiquimod-related impurities in an amount of no more than about 0.15% wt./wt. after storage of said pharmaceutical cream at ambient conditions for at least about 2 months at about 40° C and about 75% humidity, when absorbance of said pharmaceutical cream is analyzed at about 308 nm using a UV detector.	Because Nycomed's generic imiquimod-oleic acid cream formulation contains the same excipients as reported in Table 2 (columns C and D) of the '672 patent and an oleic acid component refined as described in ¶ 17 of the Nordsiek Affidavit, and because imiquimod is a very stable molecule, Nycomed's generic imiquimod must have imiquimod-related impurities in an amount of no more than about 0.15% wt./wt. after storage of said pharmaceutical cream at ambient conditions for at least about 2 months at about 40° C and about 75% humidity, when absorbance of said pharmaceutical cream is analyzed at about 308

	nm using a UV detector. *See '672 Patent, Table 2 (Exhibit B); Nordsiek Affidavit* ¶¶ *20-24.*
CLAIM 11	
The pharmaceutical formulation of claim 7, wherein the imiquimod is present in an amount of about 5% by weight based on the total weight of said pharmaceutical cream	Nycomed's generic imiquimod is a pharmaceutical formulation of claim 7 wherein the imiquimod is present in an amount of about 5% by weight based on the total weight of said pharmaceutical cream. *See, Appendix 3 of the Nycomed ANDA Letter of January 10, 2007 (Exhibit C); Nordsiek Affidavit at* ¶25.
and wherein the oleic acid component is present in an amount of no more than about 30% by weight based on the total.	The oleic acid component in Nycomed's generic imiquimod is present in an amount of no more than about 30% by weight based on the total. *See, Appendix 3 of the Nycomed ANDA Letter of January 10, 2007 (Exhibit C); Nordsiek Affidavit at* ¶26.
CLAIM 13	
A pharmaceutical cream for topical application to a dermal or mucosal surface for topical delivery of 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine (imiquimod), said pharmaceutical cream comprising:	Nycomed's generic imiquimod is a pharmaceutical cream for topical application to a dermal or mucosal surface for topical delivery of 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine (imiquimod). *See, Appendix 3 of the Nycomed ANDA Letter of January 10, 2007 (Exhibit C); Nordsiek Affidavit at* ¶11.
a therapeutically effective amount of	Nycomed's generic imiquimod includes 5%

imiquimod; and	imiquimod. This is a therapeutically effective amount of imiquimod. *See Appendix 3 of the Nycomed ANDA Letter (Exhibit C); Nordsiek Affidavit at ¶12.*
a pharmaceutically acceptable vehicle including an oleic acid component,	Nycomed's generic imiquimod uses a pharmaceutically acceptable vehicle including an oleic acid component. *See Appendix 3 of the Nycomed ANDA Letter (Exhibit C); Nordsiek Affidavit at ¶13.*
wherein the oleic acid component at or prior to formulation of said pharmaceutical cream contains at least about 80% oleic acid by weight as a fatty acid, and	In order for the oleic acid component in Nycomed's generic imiquimod-oleic acid cream to be stable, it must comprise at least about 80% oleic acid by weight as a fatty acid. *Nordsiek Affidavit at ¶13-17, 19.*
wherein the oleic acid component at or prior to formulation of said pharmaceutical cream has a peroxide value of less than about 5 milliequivalents of oxygen per kilogram and contains less than about 1% by weight polar impurities, and	In order for the oleic acid component in Nycomed's generic imiquimod-oleic acid cream to be stable, it must have a peroxide value of less than about 5 milliequivalents of oxygen per kilogram, and contain less than about 1% by weight polar impurities. *Nordsiek Affidavit at ¶¶13-17, 19.*
wherein said pharmaceutical cream contains imiquimod-related impurities in an amount of no more than about 0.29% wt./wt. after storage of said pharmaceutical cream at ambient conditions for at least about 4 months at about 40° C and about 75% humidity, when	Because Nycomed's generic imiquimod-oleic acid cream formulation contains the same excipients as reported in Table 2 (columns C and D) of the '672 patent and an oleic acid component refined as described in ¶ 17 of the Nordsiek Affidavit, and because imiquimod is

absorbance of said pharmaceutical cream is analyzed at about 308 nm using a UV detector.	a very stable molecule, Nycomed's generic imiquimod must have imiquimod-related impurities in an amount of no more than about 0.29% wt./wt. after storage of said pharmaceutical cream at ambient conditions for at least about 4 months at about 40° C and about 75% humidity, when absorbance of said pharmaceutical cream is analyzed at about 308 nm using a UV detector. *See '672 Patent, Table 2 (Exhibit B); Nordsiek Affidavit* ¶¶ *20-24.*
CLAIM 17	
The pharmaceutical formulation of claim 13, wherein the imiquimod is present in an amount of about 5% by weight based on the total weight of said pharmaceutical cream	Nycomed's generic imiquimod is a pharmaceutical formulation of claim 13 wherein the imiquimod is present in an amount of about 5% by weight based on the total weight of said pharmaceutical cream. *See, Appendix 3 of the Nycomed ANDA Letter of January 10, 2007 (Exhibit C); Nordsiek Affidavit at* ¶*25.*
and wherein the oleic acid component is present in an amount of no more than about 30% by weight based on the total.	The oleic acid component in Nycomed's generic imiquimod is present in an amount of no more than about 30% by weight based on the total. *See, Appendix 3 of the Nycomed ANDA Letter of January 10, 2007 (Exhibit C); Nordsiek Affidavit at* ¶*26.*
CLAIM 19	
The pharmaceutical cream of claim 7, wherein	Nycomed's generic imiquimod is a

said pharmaceutical cream contains imiquimod-related impurities in an amount of (a) no more than about 0.04% wt./wt. after storage of said pharmaceutical cream for at least about 2 months at about 40.degree. C. and about 75% humidity and (b) no more than about 0.04% wt./wt. after storage of said pharmaceutical cream for at least about 4 months at about 40.degree. C. and about 75% humidity, when absorbance of said pharmaceutical cream is analyzed at about 308 nm using a UV detector.	pharmaceutical cream of claim 7. Because Nycomed's generic imiquimod-oleic acid cream formulation contains the same excipients as reported in Table 2 (columns C and D) of the '672 patent and an oleic acid component refined as described in ¶ 17 of the Nordsiek Affidavit, and because imiquimod is a very stable molecule, Nycomed's generic imiquimod must have imiquimod-related impurities in an amount of no more than about 0.04% wt./wt. after storage of said pharmaceutical cream at ambient conditions for at least about 2 months at about 40° C and about 75% humidity, and no more than about 0.04% wt./wt. after storage of said pharmaceutical cream for at least about 4 months at about 40.degree. C. and about 75% humidity, when absorbance of said pharmaceutical cream is analyzed at about 308 nm using a UV detector. when absorbance of said pharmaceutical cream is analyzed at about 308 nm using a UV detector. *See '672 Patent, Table 2 (Exhibit B); Nordsiek Affidavit ¶¶ 20-24.*
CLAIM 20	
The pharmaceutical cream of claim 7, wherein said pharmaceutical cream contains imiquimod-related impurities in an amount of (a) no more than about 0.15% wt./wt. after storage of said pharmaceutical cream for at	Nycomed's generic imiquimod is a pharmaceutical cream of claim 7. Because Nycomed's generic imiquimod-oleic acid cream formulation contains the same excipients as reported in Table 2 (columns C

least about 2 months at about 40.degree. C. and about 75% humidity and (b) no more than about 0.15% wt./wt. after storage of said pharmaceutical cream for at least about 4 months at about 40.degree. C. and about 75% humidity, when absorbance of said pharmaceutical cream is analyzed at about 308 nm using a UV detector.	and D) of the '672 patent and an oleic acid component refined as described in ¶ 17 of the Nordsiek Affidavit, and because imiquimod is a very stable molecule, Nycomed's generic imiquimod must have imiquimod-related impurities in an amount of no more than about 0.04% wt./wt. after storage of said pharmaceutical cream at ambient conditions for at least about 2 months at about 40° C and about 75% humidity, and no more than about 0.04% wt./wt. after storage of said pharmaceutical cream for at least about 4 months at about 40.degree. C. and about 75% humidity, when absorbance of said pharmaceutical cream is analyzed at about 308 nm using a UV detector. when absorbance of said pharmaceutical cream is analyzed at about 308 nm using a UV detector. *See '672 Patent, Table 2 (Exhibit B); Nordsiek Affidavit ¶¶ 20-24.*

EXHIBIT 3

Guidance for Industry

Citizen Petitions and Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

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For questions regarding this draft document contact (CDER) Nancy Boocker 301-796-3601.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

Procedural

January 2009

Guidance for Industry

Citizen Petitions and Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act

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U.S. Department of Health and Human Services
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Contains Nonbinding Recommendations

Draft — Not for Implementation

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Contains Nonbinding Recommendations

Draft — Not for Implementation

Guidance for Industry[1]

Citizen Petitions and Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides information regarding FDA's (or the Agency's) current thinking on interpreting section 914 of Title IX of the Food and Drug Administration Amendments Act (FDAAA).[2] Section 914 of FDAAA adds new section 505(q) to the Federal Food, Drug, and Cosmetic Act (the Act)[3] and governs certain citizen petitions and petitions for stay of Agency action that request that FDA take any form of action related to a pending application submitted under section 505(b)(2) or 505(j) of the Act.[4]

This guidance describes FDA's interpretation of section 505(q) regarding how the Agency determines if (1) the provisions of section 505(q) addressing the treatment of citizen petitions and petitions for stay of Agency action (collectively, petitions) apply to a particular petition and (2) a petition would delay approval of a pending abbreviated new drug application (ANDA) or 505(b)(2) application. This guidance also describes how FDA interprets the provisions of section 505(q) requiring that (1) a petition include a certification and (2) supplemental information or comments to a petition include a verification[5] and addresses the relationship between the review of petitions and pending ANDAs and 505(b)(2) applications for which the Agency has not yet made a decision on approvability.

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[1] This guidance has been prepared by the Office of Regulatory Policy in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] Public Law 110-85 (as amended by Public Law 110-316).

[3] 21 U.S.C. 355(q). For brevity, in this guidance, references to section 505(q) of the Act are cited as section 505(q).

[4] 21 U.S.C. 355(b)(2) and (j). In this guidance, an application submitted under section 505(b)(2) of the Act is referred to as a 505(b)(2) application and an application submitted under section 505(j) of the Act is referred to as an abbreviated new drug application (ANDA).

[5] Section 505(q)(1)(E) provides that FDA may issue guidance to describe the factors that will be used to determine whether a petition is submitted with the primary purpose of delaying the approval of an application. This guidance does not address the factors under section 505(q)(1)(E). Any guidance issued pursuant to section 505(q)(1)(E) will be issued separately from this guidance. FDA also is considering issuing regulations through notice and comment rulemaking to further implement section 505(q).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

FDAAA was enacted on September 27, 2007. Section 914 of Title IX of FDAAA took effect on the date of enactment and amended section 505 of the Act by adding a new subsection (q). Section 505(q) applies to certain petitions that request that FDA take any form of action related to a pending ANDA or 505(b)(2) application and governs the manner in which these petitions are treated. The provisions of section 505(q) are described in greater detail below.

A. Scope of Section 505(q)

Section 505(q)(1)(A), together with section 505(q)(5), describes the general scope of section 505(q). Section 505(q)(1)(A) provides:

> The Secretary shall not delay approval of a pending application submitted under subsection (b)(2) or (j) because of any request to take any form of action relating to the application, either before or during consideration of the request, unless–
>
> (i) the request is in writing and is a petition submitted to the Secretary pursuant to section 10.30 or 10.35 of title 21, Code of Federal Regulations (or any successor regulations); and
> (ii) the Secretary determines, upon reviewing the petition, that a delay is necessary to protect the public health.

In section 505(q)(5), the term *application* is defined as an application submitted under section 505(b)(2) or 505(j) of the Act and the term *petition* is defined as a request described in 505(q)(1)(A)(i).

B. Determination of Delay

If FDA determines that a delay of approval of an ANDA or 505(b)(2) application is necessary to protect the public health, FDA is required to provide to the applicant not later than 30 days after making the determination:

1. notification that the determination has been made,
2. if applicable, any clarification or additional data that the applicant should submit to the petition docket to allow FDA to review the petition promptly, and
3. a brief summary of the specific substantive issues raised in the petition which form the basis of the determination.[6]

[6] Section 505(q)(1)(B).

At FDA's discretion, the information is to be conveyed by either a document or a meeting with the applicant.[7] The information conveyed as part of the notification is to be considered part of the application and subject to the disclosure requirements applicable to information in such application.[8]

C. Certification and Verification

Under section 505(q)(1)(H), FDA may not consider a petition for review unless the petition is in writing and signed and contains a certification that is specified in that section. In addition, FDA may not accept for review any supplemental information or comments on a petition unless the submission is in writing and signed and contains a specific verification.[9]

D. Final Agency Action

Section 505(q)(1)(F) governs the timeframe for final Agency action on a petition. Under this provision, FDA shall take final Agency action on a petition not later than 180 days after the date on which the petition is submitted. The 180-day period is not to be extended for any reason, including any determination made under section 505(q)(1)(A) regarding delay of approval of an application, the submission of comments or supplemental information, or the consent of the petitioner.

FDA may deny a petition at any point if the Agency determines that a petition or a supplement to the petition was submitted with the primary purpose of delaying the approval of an application and the petition does not on its face raise valid scientific or regulatory issues.[10] FDA may issue guidance to describe the factors that will be used to determine whether a petition is submitted with the primary purpose of delaying the approval of an application.[11]

E. Judicial Review

Section 505(q)(2) governs judicial review of final Agency action. Under section 505(q)(2)(A), FDA shall be considered to have taken final Agency action on a petition if FDA makes a final decision within the meaning of 21 CFR 10.45(d) during the 180-day period or the 180-day period expires without FDA having made a final decision. Under section 505(q)(2)(B), if a civil action is filed against the Secretary with respect to any issues raised in the petition before final Agency action, a court shall dismiss the action without prejudice for failure to exhaust administrative remedies. Section 505(q)(2)(C) describes the information to be included in the administrative record.

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[7] Section 505(q)(1)(C).

[8] Section 505(q)(1)(D).

[9] Section 505(q)(1)(I).

[10] Section 505(q)(1)(E).

[11] Section 505(q)(1)(E). As noted in footnote 5, any guidance issued pursuant to section 505(q)(1)(E) will be issued separately from this guidance.

F. Exceptions and Reporting

Section 505(q)(4) exempts certain categories of petitions from the provisions of section 505(q) — in particular, petitions relating to 180-day generic drug exclusivity and petitions from a 505(b)(2) or ANDA applicant regarding FDA actions with respect to that application. Section 505(q)(3) and section 914(b) of FDAAA also provide for certain reporting requirements from FDA to Congress.

III. DISCUSSION

As described in section II of this guidance, the provisions of section 505(q) addressing the treatment of petitions apply only to certain petitions. These provisions include, for example, the requirements that approval of an ANDA or 505(b)(2) application not be delayed by a petition absent an Agency determination that a delay is necessary to protect the public health, the provisions requiring final Agency action on the petition within 180 days of submission, and the provisions requiring a certification or a verification.

We describe below how we determine:

- if the provisions of section 505(q) apply to a particular petition
- if a petition would delay approval of a pending ANDA or 505(b)(2) application

We also describe how we interpret:

- section 505(q)(1)(H) requiring that a petition include a certification
- section 505(q)(1)(I) requiring that supplemental information or comments on a petition include a verification

We also describe the relationship between the review of petitions under section 505(q) and the review of ANDAs and 505(b)(2) applications for which the Agency has not yet made a final decision on approvability.

A. How Does FDA Determine if Section 505(q) Applies to a Particular Petition?

We interpret section 505(q) to apply to a petition only if the petition meets all of the following criteria:

- The petition is submitted to FDA on or after September 27, 2007.
- The petition is submitted in writing and pursuant to 21 CFR 10.30 or 10.35.
- An ANDA or 505(b)(2) application is pending at the time the petition is submitted to FDA.
- The petitioner requests an action that could delay approval of a pending ANDA or 505(b)(2) application.
- The petition does not fall within any of the exceptions described in section 505(q)(4).

We discuss each criterion in greater detail below.

1. Petition Submitted on or after September 27, 2007

Because section 914 of FDAAA became effective on September 27, 2007, we believe that the provisions of section 505(q) only apply to petitions that are submitted on or after September 27, 2007. We do not believe that section 505(q) applies to any petitions that were submitted before September 27, 2007, because section 505(q) does not state that it applies retroactively to petitions submitted before the effective date. In addition, such an interpretation might impose a 180-day deadline for responding to a petition after the 180 days have already expired.

Even if section 505(q) were interpreted to retroactively apply to pre-September 27, 2007, petitions, FDA would not be able to review any petition submitted before September 27, 2007, because those petitions would not contain the required certification and, as explained in section III.C of this guidance, the statute does not permit a petitioner to cure the deficiency by supplementing a pre-September 27, 2007, petition to add the certification to the petition.

2. Petition Submitted in Writing and Pursuant to § 10.30 or 10.35

Under section 505(q) of the Act, a petition must be submitted in writing and pursuant to § 10.30 or 10.35. Section 10.30 of our regulations describes FDA's general requirements for submitting a citizen petition, and § 10.35 describes our requirements for submitting a request for administrative stay of action. If these criteria are not met, we will not consider section 505(q) to apply to the petition.

We note that communications with the Agency regarding any issues intended to delay the approval of an ANDA or 505(b)(2) application (regardless of whether the communications are considered to be petitions subject to section 505(q)) are appropriately submitted through the petition process pursuant to § 10.30 or 10.35 rather than as correspondence to the NDA, ANDA, or 505(b)(2) application or another process. Similarly, any communications regarding a citizen petition should be filed as comments in the appropriate docket, not to the NDA, ANDA, or 505(b)(2) application.

We also remind persons that they may not cross-reference or rely upon information that is not included in the petition. Under §§ 10.30(b) and 10.35(b), petitions must be submitted in accordance with 21 CFR 10.20. Section 10.20(c) requires that "[i]nformation referred to or relied upon in a submission is to be included in full and may not be incorporated by reference, unless previously submitted in the same proceeding." In addition, the certification required for petitions subject to section 505(q) (described in section III.C of this guidance) and the certification required for citizen petitions under § 10.30(b) require the petitioner to certify that "this petition includes all information and views upon which the petition relies." A petition therefore is required to include all information referred to or relied upon by the petitioner. In addition, the petition should contain all information, both favorable and unfavorable, regarding the petitioner's claims.

3. *ANDA or 505(b)(2) Application Is Pending at the Time the Petition Is Submitted*

Section 505(q)(1)(A) describes the scope of section 505(q) (see section II of this guidance). Section 505(q)(1)(A) specifically references pending applications and contemplates the possibility that approval could be delayed by issues raised in a petition. Therefore, we interpret section 505(q) to apply only to petitions for which, at the time the petition is submitted, at least one ANDA or 505(b)(2) application related to the subject matter of the petition is pending.[12] If there is no related ANDA or 505(b)(2) application pending at the time that the petition is submitted, then we will not consider the provisions of section 505(q) to apply to the petition. We believe this interpretation is appropriate because if no related ANDA or 505(b)(2) application is pending at the time that a petition is submitted, the references in section 505(q)(1)(A) to a pending application and delay of approval by a petition would be inapplicable.

We also believe our interpretation is appropriate to ensure the fair and orderly implementation of section 505(q). Because application of the provisions of section 505(q) flows from a determination that a petition is within the scope of section 505(q), the evaluation of whether a related ANDA or 505(b)(2) application is pending needs to be made at the time that the petition is submitted. If we were to take a "rolling" evaluation approach, the status of the petition could change at any time from one that is not subject to section 505(q) to one that is subject to section 505(q) should a related ANDA or 505(b)(2) application be submitted before we have taken final Agency action on the petition. Such a change in the status of the petition would disrupt the orderly application of the provisions of section 505(q) and also could prejudice petitioners and commenters.

For example, as described in sections III.C and D of this guidance, to be reviewed by FDA, any petition subject to section 505(q) must include a certification and any comments to a petition subject to section 505(q) must include a verification. If, after submission, a petition's status were converted from not being subject to section 505(q) to being subject to section 505(q), a petitioner who did not include a certification in the petition and/or commenter who did not include a verification in the comments would be prejudiced because the petition or the comments would not be eligible for review by FDA.

For these reasons, we interpret section 505(q) to apply only to petitions for which, at the time the petition is submitted, at least one ANDA or 505(b)(2) application related to the subject matter of the petition is pending. We recognize that petitioners may not be aware of the existence of a pending application. Therefore, we encourage all petitioners challenging the approvability of a possible ANDA or 505(b)(2) application to include the certification required in section 505(q)(1)(H).

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[12] Although the existence of a pending application generally is not made public by FDA, a potential petitioner may be aware of the existence of a pending ANDA or 505(b)(2) application, because of (1) a paragraph IV patent notification, from the applicant to the new drug application (NDA) holder and the patent owner, stating that the application has been submitted and explaining the factual and legal bases for the applicant's opinion that the patent is invalid or not infringed (see section 505(b)(2)(B) and (j)(2)(B) of the Act), (2) a public announcement by the applicant disclosing the submission of the application, or (3) the tentative approval of an ANDA or 505(b)(2) application made public by FDA or the applicant. In addition, FDA's Web site identifies drug products for which the Agency has received an ANDA with a paragraph IV certification.

4. Petition Requests an Action That Could Delay Approval of a Pending ANDA or 505(b)(2) Application

As noted, section 505(q)(1)(A) contemplates the possibility that approval of a pending ANDA or 505(b)(2) application could be delayed by issues raised in the petition.[13] Therefore, we interpret section 505(q) to apply only to petitions that request an action that could delay approval of a pending ANDA or 505(b)(2) application. If the action requested by the petition could not delay approval of the application under any reasonable theory, we will not consider the provisions of section 505(q) to apply to the petition.

5. Petition Does Not Fall Within Any of the Exceptions Described in Section 505(q)(4)

Section 505(q)(4) provides that section 505(q) will not apply to any petitions that:

1. relate solely to the timing of approval of an application pursuant to the 180-day exclusivity provision at section 505(j)(5)(B)(iv) of the Act, or
2. are from the sponsor of the ANDA or 505(b)(2) application and seek only to have FDA take or refrain from taking any action with respect to that application.

If either of these exceptions applies, we will not consider the provisions of section 505(q) to apply to the petition.

B. How Does FDA Determine if a Petition Would Delay Approval of an ANDA or 505(b)(2) Application?

Under section 505(q)(1)(A), FDA shall not delay approval of an ANDA or 505(b)(2) application because of a petition unless the Agency determines that a delay is necessary to protect the public health. To implement this provision, first we determine if the provisions of section 505(q) apply to the petition based on the criteria described in section III.A of this guidance. If the provisions apply, we then determine if the petition may be summarily denied as described in section 505(q)(1)(E) (which allows denial of a petition that was submitted with the primary purpose of delaying approval of an application and does not on its face raise valid scientific or regulatory issues).

If we do not find that the petition may be summarily denied, we will determine if the petition would be the cause of a delay in an approval of an ANDA or 505(b)(2) application by using a *but for* test. In other words, would the ANDA or 505(b)(2) application be ready for approval but for the issues raised by the petition?

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[13] We note that there are means other than submission of a petition by which interested persons can express their views on issues related to bioequivalence. FDA has been posting draft product-specific bioequivalence recommendations on its Web site at http://www.fda.gov/cder/guidance/bioequivalence/default.htm and announcing in a *Federal Register* notice the availability of these recommendations and the opportunity for the public to consider and comment on the recommendations. We encourage interested persons to submit any comments related to bioequivalence issues in response to a *Federal Register* notice announcing the recommendations.

- If, regardless of the petition, the ANDA or 505(b)(2) application would not be ready for approval, then section 505(q)(1)(A) would not be implicated.[14]

- If the ANDA or 505(b)(2) application would be ready for approval but for the petition, then we would next determine if a delay of approval is necessary to protect the public health.

We determine if a delay of approval is necessary to protect the public health based on our preliminary evaluation of the issues raised in the petition. The Agency considers the following:

> If the application were approved before the Agency completed the substantive review of the issues in the petition and, after further review, the Agency concluded that the petitioner's arguments against approval were meritorious, could the presence on the market of drug products that did not meet the requirements for approval negatively affect the public health?

If, after undertaking this analysis, we conclude that the public health could be negatively affected, the Agency will conclude that a delay "is necessary to protect the public health" and will delay approval of the pending application. Issues that could implicate the public health include, for example, (1) whether a proposed generic drug product is bioequivalent to the reference listed drug or (2) whether an indication can be safely omitted from the labeling because that indication is protected by a patent.

If we determine that a delay is necessary, we will notify the applicant as required by section 505(q)(1)(B) and (C) of the Act. Under these provisions, we are required to provide the following information to the applicant not later than 30 days after making the determination:

- Notification that the determination has been made
- If applicable, any clarification or additional data that the applicant should submit to the petition docket to allow FDA to review the petition promptly
- A brief summary of the specific substantive issues raised in the petition which form the basis of the determination

At our discretion, we will convey this information to the applicant by either a letter or a meeting with the applicant.[15] As provided in section 505(q)(1)(D), we will consider the information conveyed in the notification to be part of the application and subject to the disclosure requirements applicable to information in such application. We do not intend to notify the petitioner if a determination has been made that a delay in approval of an application is necessary to protect the public health because the provisions of section 505(q) do not require such a notification to the petitioner.

If we determine that a delay of approval is not necessary to protect the public health, we will proceed with approving the application.

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[14] We note, however, that a petition would still be subject to section 505(q) as long as a relevant application is pending at the time the petition is submitted.

[15] See section 505(q)(1)(C).

C. How Does FDA Apply the Certification Requirements in Section 505(q)(1)(H)?

Section 505(q)(1)(H) of the Act provides that FDA shall not consider a petition for review unless the petition is in writing and signed and contains the following certification:

> I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: _____[in the blank space, provide the date on which such information first became known to such party]. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: _____ [in the blank space, provide the names of such persons or organizations]. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

This certification includes statements in addition to those described under § 10.30(b) for the certification in citizen petitions.

We apply section 505(q)(1)(H) to require that all petitions that fall within the scope of section 505(q) be in writing and signed, and contain the complete 505(q) certification to be considered for review by FDA. If, based on the criteria described in section II.A of this guidance, section 505(q) applies to the petition, but the petition is not in writing or signed, or does not contain the complete certification, we will not review the petition.

We also apply section 505(q)(1)(H) to require that the certification be included in the original petition. Section 505(q)(1)(H) refers to the "petition" as the subject document that must contain the certification. Because sections 505(q)(1)(E) and 505(q)(1)(I) distinguish between petitions and supplements to petitions,[16] the reference to a petition in section 505(q)(1)(H) refers only to the original petition and not to a supplement. Therefore, if a petition is missing the complete certification, we will not permit a petitioner to cure the deficiency by submitting a supplement to add the certification to the petition.

If a petitioner has submitted a petition that is missing the required certification but is otherwise within the scope of section 505(q) and the petitioner would like FDA to review the petition, the petitioner should (1) submit a letter withdrawing the deficient petition pursuant to § 10.30(g) and (2) submit a new petition that contains the certification. In this case, the provisions of section 505(q) governing the treatment of petitions will apply only to the new petition that includes the required certification because we cannot review the deficient petition under section 505(q)(1)(H).

[16] Section 505(q)(1)(E) states that if FDA determines that a petition or a supplement to the petition was submitted with the primary purpose of delaying approval of an application, the Agency may deny the petition at any point. Section 505(q)(1)(I) requires that supplemental information include a verification as described in section III.D of this guidance.

In particular, we consider the 180-day timeframe for FDA to respond to the petition to begin from the date of submission of the new, complete petition and not the original, deficient petition.

Because FDA will not review a petition that is subject to section 505(q) but is missing the required certification, we strongly encourage all petitioners raising issues that could delay the approval of a possible ANDA or 505(b)(2) application to include the certification in their petitions to ensure FDA consideration. Although we may contact a petitioner to notify him or her of a missing or deficient certification, we note that it is the responsibility of the petitioner to ensure that its petition complies with the applicable requirements of section 505(q), as well as all other applicable statutory and regulatory requirements.

D. How Does FDA Apply the Verification Requirements in Section 505(q)(1)(I)?

Section 505(q)(1)(I) provides that FDA shall not accept for review any supplemental information or comments on a petition unless the supplemental information or comments are in writing, signed, and contain the following verification:

> I certify that, to my best knowledge and belief: (a) I have not intentionally delayed submission of this document or its contents; and (b) the information upon which I have based the action requested herein first became known to me on or about _____[in the blank space, provide the date on which such information first became known to such party]. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: _____ [in the blank space, provide the names of such persons or organizations]. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Section 505(q)(1)(I) applies to any supplemental information or comments that are submitted to a petition that is subject to section 505(q). If any such supplemental information or comments do not include the required verification, FDA will not review the submission.

If a petitioner or commenter has submitted supplemental information or comments without the required verification or with an incomplete verification and the petitioner or commenter would like FDA to review the submission, the petitioner or commenter should resubmit the supplemental information or comments with the required verification to FDA.

For petitions that are subject to section 505(q), because FDA will not review any supplemental information or comments that are missing the required verification, we strongly encourage all petitioners or commenters to include the verification in their supplemental information or comments to a petition that includes the 505(q) certification to ensure FDA consideration. We will not notify petitioners and commenters of a missing or deficient verification. In some instances, FDA receives numerous supplements and comments in a docket, and it would be administratively burdensome to monitor all the dockets for 505(q) petitions and notify commenters about the statutory requirement. It is the responsibility of petitioners and commenters to ensure that their supplemental information or comments comply with the applicable requirements of section 505(q), as well as all other applicable statutory and regulatory requirements.

E. What Is the Relationship Between the Review of Petitions Under Section 505(q) and the Review of ANDAs and 505(b)(2) Applications for Which the Agency Has Not Yet Made a Final Decision on Approvability?

A petition may request that FDA take an action related to a specific aspect of a pending ANDA or 505(b)(2) application for which the Agency will not have made a final decision regarding approvability by the date that the petition response is due. As described in section II.D., section 505(q)(1)(F) requires FDA to take final Agency action on a petition within 180 days of submission. The review of applications that may be affected by the petition is governed by a separate review process, which will not necessarily be completed by the date the petition response is due. If a petition requests that the Agency take an action related to a specific aspect of a pending application, we will consider the review status of the affected application(s) in determining whether it would be appropriate for the Agency to respond to the request to take the action requested in the petition within the 180-day timeframe.

The provisions in section 505 of the Act and FDA's regulations at 21 CFR part 314 establish certain procedures by which the Agency reviews an NDA or ANDA and notifies an applicant if it determines that an application is approved (§ 314.105) or may not be approved (section 505(c) and 505(j); §§ 314.125 and 314.127), or identifies the deficiencies in the application and the steps an applicant may take to respond to the deficiencies (§ 314.110). In addition, the statute and regulations describe a specific process through which an applicant whose application the Agency has found not to meet the requirements for approval may challenge the Agency's determination (section 505(c)(1)(B) and (d), 505(j)(5)(E); § 314.200). Under this process, the Agency must give the applicant notice of an opportunity for a hearing on whether the application is approvable, with a specific timeframe and process should the applicant request such a hearing. These procedures ensure that applicants have an adequate opportunity to challenge a finding by the Agency that a product does not meet the requirements for approval.

By contrast, responses to citizen petitions, including petitions subject to section 505(q), constitute final Agency action and are subject to immediate review by the courts. They therefore carry with them none of the procedural rights for the affected applicants that attach to a decision to deny approval of an application. If we were to respond substantively a petitioner's request regarding the approvability of a certain aspect of a pending application before we have taken a final action on the approvability of the application as a whole, such response could interfere with the statutory and regulatory scheme governing the review of applications and related procedural rights of applicants.[17] There is no evidence that in enacting section 505(q), Congress intended to limit applicants' procedural rights by requiring that the Agency make decisions that constitute final Agency action on the approvability of specific aspects of a pending application (e.g., the acceptability of a proposed trade name, specific claims proposed in a drug product's labeling) on a piecemeal basis outside of the process established under the Act and regulations.[18]

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[17] We also note that under applicable statutory and regulatory provisions, we are generally prohibited from disclosing information regarding applications that have not yet been approved. Depending upon the nature and specificity of a petition, these limitations on disclosure also may circumscribe the Agency's ability to respond substantively to issues raised in a petition that affect a pending application.

[18] In the past, we have responded to requests related to general standards for approval (e.g., bioequivalence criteria for generic drug products or the appropriateness of omitting certain protected information from proposed drug

Therefore, we do not interpret section 505(q) to require a substantive final Agency decision within 180 days on the approvability of a specific aspect of a pending application when a final decision on the approvability of the application as a whole has not yet been made and when to render such a decision could deprive an applicant of procedural rights established by statute and regulations. In such a situation, we would expect to deny a petition without comment on the substantive approval issue.

product labeling) that may pertain to one or more pending drug applications, without commenting on the approvability of any particular aspect of a specific pending application. We distinguish our approach of responding to petitions that involve general policies or standards for approval of a drug application from our approach described above, which applies to petitions that involve narrow issues of approvability of a specific aspect or aspects of a pending application. We will continue to evaluate each citizen petition on a case-by-case basis with respect to the appropriateness of responding to the petitioner's requests vis-à-vis any pending applications.

EXHIBIT 4

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

SEP 13 2005

4842 5 SEP 16 A9:39

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Re: Docket No. 2005P-0127/CP1

Dear Mr. Safir:

This responds to your citizen petition dated March 31, 2005 (Petition), and your related comment dated June 10, 2005 (Comment), both submitted on behalf of Aventis Pharmaceuticals Inc. (Aventis), concerning the approval of abbreviated new drug applications (ANDAs) for leflunomide. Aventis holds the new drug application (NDA 20-905) for the reference listed drug (RLD) for leflunomide, which is marketed under the brand name Arava. Arava is commercially available in 10-milligram (mg) and 20-mg strengths. Aventis also distributes 100-mg tablets, not available in pharmacies, but available free to physicians in blister packs of three tablets.

In the Petition, you request that (1) if an ANDA applicant is not seeking approval of a 100-mg leflunomide tablet that is bioequivalent to Arava 100-mg tablets, the Food and Drug Administration (FDA or the Agency) require the applicant to perform in vivo bioequivalence testing to confirm that five of its 20-mg tablets are bioequivalent to one Arava 100-mg tablet, and (2) the Agency withhold final approval of any leflunomide ANDA that either (a) does not seek approval of a 100-mg leflunomide tablet that is bioequivalent to Arava 100-mg tablets or (b) does not establish in vivo bioequivalence between five 20-mg leflunomide tablets and one Arava 100-mg tablet.

For the reasons that follow, the Petition is denied. This decision is based on a review of the Petition and the comments submitted in response to it,[1] as well as other information available to the Agency. Generic leflunomide product lines that provide the 10-mg and/or 20-mg strengths that contain the same labeling as Arava are not compelled to also provide the 100-mg tablet. Moreover, a generic sponsor of a 20-mg leflunomide tablet who has demonstrated bioequivalence to Arava 20-mg tablets, is not also required to demonstrate bioequivalence of five of the 20-mg generic leflunomide product to one Arava 100-mg tablet.

[1] These include comments submitted by Kali Laboratories, Inc. (Kali), dated May 12, 2005 (2005P-0127/C1), comments submitted by Olsson, Frank and Weeda, P.C., dated May 18, 2005 (2005P-0127/C2), and your Comment referenced above (2005P-0127/RC1).

2005P-0127

PDN 1

I. BACKGROUND

A. Factual Information

Leflunomide (Arava) is a pyridimine synthesis inhibitor that is indicated in adults for the treatment of active rheumatoid arthritis (RA) to reduce signs and symptoms and to retard structural damage. Leflunomide is metabolized to one primary active metabolite (M1) that is responsible for essentially all of its in vivo activity. M1 is eliminated by further metabolism and subsequent renal excretion as well as by direct biliary excretion. M1 has a half-life of 15 days. The usual daily dose of leflunomide is 20 mg. Because of the long half-life of M1, however, a loading dose of 100 mg per day for 3 days is recommended in Arava's approved labeling to quickly reach steady state plasma concentrations of M1. The use of a loading dose is not essential to the effective use of the product, and elimination of the loading dose may decrease the risk of adverse events.[2]

Bioequivalence between five 20-mg tablets and one 100-mg tablet of Arava has not been established. Arava 100-mg tablets have a formulation that is not proportionally similar relative to either the 20-mg or the 10-mg tablets.[3] FDA's publication *Approved Drug Products With Therapeutic Equivalence Evaluations* (commonly referred to as the Orange Book) lists both the 20-mg and the 100-mg tablets of Arava as the reference listed drugs (RLDs) for leflunomide tablets. FDA would not waive the requirement for the submission of evidence measuring the in vivo bioequivalence of five 20-mg leflunomide tablets (or ten 10-

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[2] The *DOSAGE AND ADMINISTRATION* portion of Arava's labeling states in part the following:

> **Loading Dose**
> Due to the long half-life in patients with RA and recommended dosing interval (24 hours), a loading dose is needed to provide steady-state concentrations more rapidly. It is recommended that ARAVA therapy be initiated with a loading dose of one 100 mg tablet per day for 3 days.
> Elimination of the loading dose regimen may decrease the risk of adverse events. This could be especially important for patients at increased risk of hematologic or hepatic toxicity, such as those receiving concomitant treatment with methotrexate or other immunosuppressive agents or on such medications in the recent past (see **WARNINGS — Hepatotoxicity**).

Loading dose is also referred to in the following portion of the labeling:

> **Absorption**
> Following oral administration, peak levels of the active metabolite, M1, occurred between 6 - 12 hours after dosing. Due to the very long half-life of M1 (~2 weeks), a loading dose of 100 mg for 3 days was used in clinical studies to facilitate the rapid attainment of steady-state levels of M1. Without a loading dose, it is estimated that attainment of steady-state plasma concentrations would require nearly two months of dosing. The resulting plasma concentrations following both loading doses and continued clinical dosing indicate that M1 plasma levels are dose proportional.

[3] The 20-mg and 10-mg tablets are proportionally similar (see NDA 20905, Clinical Pharmacology and Biopharmaceutics Review(s) (attached at Tab 2 to the Petition) at 3). The 100-mg and 20-mg tablets are not proportionally similar (see Leflunomide Tablets, NDA Amendment/Biopharmaceutical Information, NDA #20-[90]5, enclosed with letter dated June 23, 1998, from Quintiles to Sandra Cook, Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products, FDA (attached at Tab 3 to the Petition) at 10). For a detailed definition of *dose proportionality*, see p. 11 of the guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations*. Proportionality and nonproportionality of dosage strengths are important when considering bioequivalence requirements (e.g., when granting waivers of in vivo bioequivalence studies for a lower strength or strengths of a drug product).

mg tablets) and a 100-mg tablet if an ANDA applicant proposed to recommend using five 20-mg tablets (or ten 10-mg tablets) instead of a 100-mg tablet for the loading dose.

Arava was approved on September 10, 1998, at 10-mg, 20-mg, and 100-mg strengths.[4] As a new chemical entity, Arava had 5-year exclusivity under section 505(j)(5)(F)(ii) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355 (j)(5)(F)(ii)), during which time no generic applications could be submitted.[5] Because FDA determined under section 505A of the Act that Arava was entitled to pediatric exclusivity, the period of exclusive marketing was extended 6 months (i.e., until March 10, 2004).[6]

In January 2002, in a letter to pharmaceutical buyers, Aventis announced its decision "to discontinue [the] 100 mg Arava® (leflunomide) tablets trade package."[7] As your Comment acknowledges, Aventis no longer *sells* the 100-mg strength of the product (Comment at 2). Aventis does, however, continue to make the 100-mg product available free to physicians (*Id.*).[8] As acknowledged in comments submitted to the docket, generic drug applicants seek approval of the 10-mg and 20-mg strengths of leflunomide.

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[4] In 2002, in a citizen petition, Public Citizen asked the Agency to remove Arava from the market, based on the claim that its adverse events compared unfavorably with older treatments for rheumatoid arthritis. In 2003, an advisory committee meeting was held to consider the safety of the product. On March 23, 2004, in a formal response to the 2002 citizen petition, FDA announced that it continues to regard the product as safe (see Docket No. 2002P-0139/CP1).

[5] Arava also had 5-year exclusivity under section 505(c)(3)(E)(ii) of the Act. The Act's 5-year exclusivity provisions state that no ANDA (or new drug application under section 505(b)(2) of the Act (505(b)(2) application)) that references an NDA with such exclusivity can be submitted to FDA for 5 years after the date of approval of the NDA, except that an ANDA (or 505(b)(2) application) can be submitted 4 years after the date of the NDA's approval if it contains a certification stating that one or more patents claiming the drug described in the NDA, or use thereof, is invalid or not infringed (a paragraph IV certification) (see sections 505(j)(5)(F)(ii) and 505(c)(3)(E)(ii) of the Act). Such patents are listed in the Orange Book. Although a patent had been previously listed in the Orange Book for Arava, no patents were listed for Arava on or after the fourth anniversary of its approval, and no paragraph IV certifications were submitted in any ANDA for a generic leflunomide product. Accordingly, Arava enjoyed the full 5-year period of marketing exclusivity afforded by sections 505(j)(5)(F)(ii) and 505(c)(3)(E)(ii) of the Act.

[6] Your Petition was submitted approximately one year after this date. One commenter notes (see 2005P-0127/C1 at 1) that this would be at the end of the normal ANDA review cycle for an ANDA submitted on or near the date ANDAs were first eligible for submission, suggesting that the Petition intends (at least in part) to delay generic competition. We also note that the majority of the citations in your Petition are many years old, and were available to Aventis well before the petition was submitted.

[7] See http://www.aventis.custservices.com/news.asp?up=103. For a brief time FDA listed the 100-mg Arava product in the *Discontinued Drug Product List* of the Orange Book, but it is now listed again in the Orange Book's main *Prescription Drug Product List.*

[8] See also http://www.arava.com/professional/about_arava/initiation.do?warning=1.

B. Relevant Statutory Background

1. Summary of Approval Process

Under the Act, sponsors seeking to market innovator drugs must first obtain FDA approval by filing an NDA. NDAs contain, among other things, extensive scientific data demonstrating the safety and effectiveness of the drug (see sections 505(a) and (b) of the Act). The NDA applicant is also required to submit certain patent information to FDA; the Agency publishes patent information for approved drugs in the Orange Book.

The Act permits applicants to submit ANDAs for approval of generic versions of approved drug products (see section 505(j) of the Act). The ANDA process shortens the time and effort needed for approval by, among other things, allowing the applicant to demonstrate that its drug product is bioequivalent to the innovator drug, rather than reproduce the safety and effectiveness data for the innovator drug (see *Eli Lilly and Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990)). The timing of approval of an ANDA depends in part on statutory patent listing, patent certification, and exclusivity protections added to the Act by the 1984 Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Amendments), Pub. L. No. 98-417, 98 Stat. 1585. As mentioned above, by operation of the exclusivity protections afforded under the Act, ANDAs for leflunomide were not eligible for submission until March 10, 2004.

2. Summary of Statutory and Regulatory Standards

The Act generally requires an ANDA applicant to provide, among other things, information to show that the generic drug is bioequivalent[9] to the RLD (see 21 U.S.C. 355(j)(2)(A)(iv)). When there are multiple strengths of a product, this refers to bioequivalence between the same strength of the ANDA product and the RLD.[10,11] There is no requirement for an ANDA sponsor to

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[9] Section 505(j)(8)(B) of the Act provides that a generic drug shall be considered to be bioequivalent to the listed drug if:

> (i) the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or (ii) the extent of absorption of the drug does not show a significant difference from the extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the listed drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

[10] The preamble to our 1992 final rule on ANDAs explains that, "In some instances, such as the submission of an ANDA for a product with multiple strengths, there may be more than one reference listed drug. In these instances, FDA considers each strength to represent a different drug product and will require an ANDA applicant to demonstrate that each proposed drug product is bioequivalent to its corresponding reference listed drug" (*Abbreviated New Drug Application Regulations*; Final Rule, 57 FR 17950, April 28, 1992).

[11] Often the showing of bioequivalence can be accomplished without the submission of an in vivo study. FDA's regulations describe when FDA may waive in vivo bioequivalence studies on different strengths of a drug in the same dosage form:

> The drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients to another drug product for which the same manufacturer has obtained approval and the conditions in paragraphs (d)(2)(i) through (d)(2)(iii) of this section are met:

demonstrate equivalence between different strengths of its own product line.[12] Assuming that the other requirements applicable to ANDAs (which are not at issue here) are satisfied, FDA must approve the ANDA unless the information submitted in the ANDA is insufficient to show that the generic drug is bioequivalent to the RLD (see 21 U.S.C. 355(j)(4)(F)).

The Act also requires an ANDA applicant to provide, among other things, information to show that the labeling proposed for the generic drug is the same as the labeling approved for the RLD, except for changes required because of differences approved under an ANDA suitability petition or because the generic drug and the RLD are produced or distributed by different manufacturers (see 21 U.S.C. 355(j)(2)(A)(v)). Examples of these changes are listed at 21 CFR 314.94(a)(8)(iv), although this list is not exhaustive.[13] Differences in labeling that may result because a generic drug and the RLD are produced or distributed by different manufacturers include, but are not limited to, differences in the labeled name, address, and phone number for the drug manufacturer; differences in labeled colors; differences in the labeled indications for the drug (e.g., if the RLD had existing exclusivity for a particular indication); and differences in the drug's labeled strengths (e.g., if a generic manufacturer does not seek approval for all strengths approved for the RLD) (this point is discussed further in section II below).

II. DISCUSSION

You believe that FDA has accepted ANDAs seeking to market 10-mg and 20-mg tablets but not 100-mg tablets of leflunomide. You claim that the products described in these ANDAs would have no 100-mg tablets to refer to in their labeling (Petition at 2). You maintain that the approved labeling for Arava contains important dosage and administration information regarding a 100-mg loading dose and that leflunomide ANDAs must likewise contain such labeling (Petition at 4-5). You assert that this information is not the type of information that can be omitted from ANDA labeling simply because the reference drug and the ANDA drug are

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(i) The bioavailability of this other drug product has been measured;
(ii) Both drug products meet an appropriate in vitro test approved by FDA; and
(iii) The applicant submits evidence showing that both drug products are proportionally similar in their active and inactive ingredients.

(21 CFR 320.22(d)(2)).

[12] Both the Act and the bioequivalence regulations (see 21 CFR Part 320) refer only to bioequivalence between the subject of the ANDA and the RLD.

[13] See, e.g., February 15, 2002, response to Donald O. Beers, David E. Korn, William J. McNichol, Marc J. Scheineson, and Tracy Zurzolo Frisch regarding Docket Nos. 00P-1550/CP1 & PSA1 and 01P-0428/CP1 & PSA1 concerning generic cefuroxime axetil products, at 18 ("The plain language of § 314.94(a)(8)(iv) explicitly recognizes that these differences listed in the regulation are examples; therefore, § 314.94(a)(8)(iv) recognizes that there are other differences in labeling between generic drug products and reference listed drugs that are permissible due to the fact that the generic drug product and reference listed drug product are produced or distributed by different manufacturers").

produced or distributed by different manufacturers and the ANDA manufacturer does not make a 100-mg tablet (Petition at 3 and Comment at 3). Finally, you claim that omission of the loading dose information may render the generics less effective than Arava (Petition at 3 and Comment at 3).

Your argument seems to be based on a false premise, namely, that if a particular generic manufacturer recommends in leflunomide labeling a loading dose of 100 mg for three days (3 x 100 mg), the manufacturer either must (1) provide its own 100-mg product or (2) recommend using five of its 20-mg tablets. You incorrectly speculate that generic sponsors will attempt to either replace the 100-mg tablet loading dose with a loading dose of five 20-mg tablets or remove mention of the loading dose from the label (Petition at 3). In the rest of the Petition, as well as in your Comment, you argue that replacing the 100-mg loading dose with a loading dose of five 20-mg tablets should require an in vivo bioequivalence study, and that it is legally and medically inappropriate to remove mention of the loading dose from the label. You seem to ignore a third possibility: that the labeling for a generic leflunomide product can recommend a loading dose of 3 x 100 mg that can be accomplished by the use of an approved 100-mg tablet from a different manufacturer. Given the unusual manner in which the 100-mg tablet for the loading dose has been distributed by Aventis (i.e., in blister packs of 3, for free and only to, and at the request of, a physician) and the fact there are circumstances when a loading dose should perhaps not be used, we do not find it unreasonable for a generic manufacturer to elect to market only the other dosage strengths.

A generic sponsor that markets only 20-mg and 10-mg leflunomide tablets must have the same labeling as the RLD, except for differences that would be permitted under 21 U.S.C. 355(j)(2)(A)(v), discussed in subsection I.B.2 above. As does the approved labeling for Arava (see footnote 2, *supra*), approved labeling for generic leflunomide products would include the recommendation of using 100-mg tablets for the loading dose. The 100-mg tablets could be either 100-mg Arava tablets or 100-mg generic tablets from a different sponsor that have been demonstrated to be bioequivalent to the 100-mg Arava tablets.[14] We agree that changes in labeling resulting from a difference in manufacturers must not render the proposed generic drug product less safe or effective than the RLD. But we do not see this as an issue here, for we do not intend to permit the labeling regarding use of a 100-mg tablet for the loading dose to be omitted, as you surmise (see Petition at 3 and 5); nor do we see that any change not permitted by the Act is needed in this labeling if a generic manufacturer chooses to market only the 20-mg and 10-mg strengths of leflunomide.

Labeling for generic leflunomide products approved in 10- and 20-mg strengths may reference a 100-mg leflunomide tablet that the generic sponsor does not produce. As reflected by existing precedents, ANDA sponsors may refer in their labeling to products they do not manufacture. For example, the product labeling for the anti-retroviral drug Videx (didanosine) delayed-release capsules makes reference to the package inserts for Videx chewable/dispersible tablets and

[14] Your Comment acknowledges that an ANDA applicant that seeks approval of a 20-mg leflunomide tablet, but not a 100-mg tablet, could propose to "reference [in the drug's label] a 100 mg tablet that the generic does not manufacture" (Comment at 3). You go on to assert that this option should not be permitted (*Id.*); however, you provide no explanation for your assertion, and, for the reasons discussed in the text above, we see no reasoned basis to accept it.

Videx pediatric powder for oral solution for information regarding the pediatric dose. Currently, the only approved generic didanosine (Barr ANDA 77-167) is for a delayed-release capsule, which has labeling that makes reference to the other Videx dosage forms, even though Barr does not itself provide these other dosage forms. It is also not uncommon for brand name products to refer in their labeling to other drugs that are not provided by the sponsor of the brand name product (e.g., the labeling of Oncaspar, an Aventis product, recommends its use in combination with the following products not made by Aventis: vincristine, methotrexate, cytarabine, daunorubicin, and doxorubicin; also, the labeling of Eloxatin, owned by Sanofi-Synthelabo, Inc., recommends that it be used in combination with infusional 5-FU/LV[5-fluorouracil/leucovorin], which Sanofi-Synthelabo, Inc., does not supply).

Additionally, there is nothing in the Act or the regulations that requires an ANDA applicant to seek approval for all available strengths of the RLD. Both the Act and the regulations state that the generic product must be the same strength (singular) as the listed drug (see 21 U.S.C. 355(j)(2)(A)(iii) and 21 CFR 314.92 and 314.94(a)(6)(i)), implying that each strength of a reference product is in some regards a separate listed drug (see footnote 10, *supra*). It is not unusual for an ANDA applicant to decline to seek approval for certain strengths approved for the RLD (see the June 11, 2002, response in Docket Nos. 01P-0495, 02P-0191, and 02P-0252, in which FDA permitted ANDAs for tramadol that do not provide a low dose for titration that is provided by the manufacturer of the RLD). The following products are all examples from the Orange Book (2004 printed edition) in which at least one generic manufacturer has omitted at least one strength of the RLD: alprazolam tablets, amitriptyline hydrochloride tablets, haloperidol tablets, hydralazine hydrochloride tablets, hydrochlorothiazide tablets, meclizine hydrochloride tablets, mirtazapine orally disintegrating tablets, nefazadone hydrochloride tablets, nifedipine capsules, nitrofurantoin (macrocrystaline) capsules, propranolol hydrochloride tablets, trazadone hydrochloride tablets, and thioridazine hydrochloride tablets.[15] It should be noted that the reverse may also be true (i.e., the reference product may not provide strengths that a generic applicant provides (e.g., methyldopa tablets, propranolol hydrochloride tablets)).

In light of the discussion above, FDA will require the labeling for generic leflunomide products to include the labeling approved for the RLD, Arava, concerning the use of a 100-mg loading dose. Thus, your concern that (1) this labeling will be omitted for generic leflunomide products that are approved at only 10-mg and 20-mg strengths, or (2) the labeling will be changed to recommend the use of five 20-mg tablets instead of a 100-mg tablet absent appropriate bioequivalence data, is unfounded.

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[15] You state in your Comment that another example cited by Kali in its comments on the Petition (2005P-0127/C1), oxycodone hydrochloride extended release (ER) tablets, "is inapposite" because dose proportionality and/or bioavailability were established for each strength of the RLD (Comment at 3). You note that, in the case of leflunomide, dose proportionality has not been established for all of the RLD's approved strengths (*Id.*). However, while, as you acknowledge, the labeling for the generic oxycodone hydrochloride ER product includes (as does the labeling for its RLD) a statement asserting that dose proportionality and/or bioavailability have been established for all available strengths at which the RLD is approved, there is no such claim in the approved labeling for Arava. Therefore, an applicant seeking approval for generic leflunomide tablets need not establish dose proportionality for all of Arava's approved strengths; nor, as explained above, must it demonstrate bioequivalence of five 20-mg generic leflunomide tablets (or ten 10-mg tablets) to one Arava 100-mg tablet.

III. CONCLUSION

It is not necessary for a generic leflunomide sponsor to either produce a 100-mg tablet or demonstrate bioequivalence of five 20-mg tablets to one 100-mg Arava tablet. A generic leflunomide product that refers in its labeling to a 100-mg tablet (which is available from Aventis) as the loading dose will be appropriately labeled with respect to the loading dose. For these reasons your Petition is denied.

Sincerely,

Steven K. Galson, M.D., M.P.H.
Director
Center for Drug Evaluation and Research